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XCIV. A NEW APPROACH TO THE PROBLEM OF DISSEMINATED NEURODERMATITIS

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AND
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ST. LOUIS

Chronic disseminated neurodermatitis, or atopic dermatitis, as it is called in the more recent literature, has long been recognized as a distinct, well defined clinical entity. The older writers, Vidal,[1] Brocq and Jacquet,[2] Besnier,[3] Czerny [4] and others, have given accurate descriptions of its symptoms and clinical course and have propounded theories as to its cause. Some of these older writers tended to include the localized types of lichenification with disseminated dermatitis, but this confusion has been clarified by several of the modern observers, such as Sulzberger [5] and Brunsting,[6] who have shown that lichen simplex chronicus or localized neurodermatitis and chronic disseminated neurodermatitis are not identical.

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Studies, observations and reports from the Department of Dermatology of the Barnard Free Skin and Cancer Hospital and the Anatomical Laboratory, Washington University School of Medicine.

Dr. E. V. Cowdry gave advice and guidance. Drs. H. A. Bulger, R. L. Kile and P. J. Catinella gave cooperation and clinical assistance. Dr. Gordon H. Scott placed at our disposal the facilities and equipment in his laboratory.

1. Vidal, E.: Du lichen, Ann. de dermat. et syph. **7**:133, 1886.

2. Brocq, L., and Jacquet, L.: Notes pour servir à l'histoire des névrodermites, Ann. de dermat. et syph. **2**:193, 1891.

3. Besnier, E.: Première note et observations préliminaires pour servir d'introduction à l'étude des prurigos diathésiques (dermatites multiformes prurigineuses chroniques exacerbantes et paroxystiques, du type du prurigo de Hebra), Ann. de dermat. et syph. **3**:634, 1892.

4. Czerny, A.: Die exudative Diathese, Jahrb. f. Kinderh. **61**:199, 1905.

5. (*a*) Sulzberger, M. B., in discussion on Brunsting.[6] (*b*) Hill, L. W., and Sulzberger, M. B.: Evolution of Atopic Dermatitis, Arch. Dermat. & Syph. **32**: 457 (Sept.) 1935.

6. Brunsting, L. A.: Atopic Dermatitis (Disseminated Neurodermatitis) of Young Adults, Arch. Dermat. & Syph. **34**:935 (Dec.) 1936.

Disseminated neurodermatitis begins usually in infancy as an acute or chronic dermatitis distributed characteristically over the cheeks and extensor surfaces of the arms and legs or in some instances widely generalized. The infantile form undergoes exacerbations and remissions as does the adult and is usually just as resistant to treatment. More or less permanent remission finally occurs. The patient may remain normal as far as neurodermatitis is concerned for the rest of his life, or the disease may recur in its adult form. Usually recurrence appears at puberty or shortly thereafter, but in some instances it may be much earlier or much later.

In the adult phase of disseminated neurodermatitis the characteristic lesion is a chronic inflammation of the skin or chronic dermatitis with lichenification. The typical distribution is on the forehead, eyelids, sides of the face and sides of the neck and in the cubital and popliteal spaces. Exacerbations and remissions are the rule rather than the exception. During acute exacerbations there is intense pruritus in the involved areas, which results in scratching, rubbing and chemical traumas in the form of strong local applications. The areas of chronic dermatitis then become "eczematized" and present a picture of acute inflammation, with weeping, crusting and excoriation.

Pigmentary abnormalities are frequent, especially in quiescent or in healed areas. There may be hyperpigmentation or in some instances depigmentation. Careful examination of the entire body of a patient with neurodermatitis will sometimes reveal a generalized increase in pigment, not as a spotty pigmentation but as a sort of greenish sallow color of the whole skin. The skin itself, even where there has never been any dermatitis, is thicker and tougher than that of the average person. This is particularly noticeable when one takes a specimen for biopsy.

Treatment in general is most unsatisfactory. The disease seems to get better or worse irrespective of treatment. We have never found allergic regimens to be of any benefit. Our most promising results have been obtained with prolonged courses of iron cacodylate given intravenously. Remissions may sometimes be produced with this drug which will last for varying lengths of time. Ultimately the prognosis is good. Spontaneous cure is the most frequent outcome.

ATOPY

Wise and Wolf,[7] Sulzberger,[5a] Brunsting [6] and others of the modern school have chosen atopic dermatitis as the best name for this disease. They emphasized what had been pointed out by many of the older

7. Wise, F., and Wolf, J.: Eczema and Its Practical Management, J. A. M. A. **111**:2106 (Dec. 3) 1938.

writers, that the dermatitis is associated with asthma, hay fever and other allergic conditions and has many features in common with allergic phenomena in general, such as hereditary background, positive reactions to passive transfer tests and so forth. We are not prepared to state that allergy is not the basis of this disease, but, since allergic studies have thrown no real light on how this dermatitis is produced and have not given any encouraging therapeutic results, we have decided to look elsewhere for possible facts as to the cause of neurodermatitis. Since the term atopic dermatitis definitely commits one to an allergic ritual of thought, we have retained Brocq's old term, chronic disseminated neurodermatitis.

NEUROGENIC POSSIBILITIES

Becker [8] and Stokes,[9] enlarging on the ideas of Vidal,[1] Brocq and Jacquet [2] and others, have developed a theory which offers a possible neurogenic basis for the disease. There is some clinical evidence which supports these theories. There is probably a basic state of increased or unstable capillary permeability in patients with neurodermatitis. The autonomic nervous system has something to do with capillary permeability, according to Peterson and Levinson.[10] We are, however, not any more satisfied with a neurogenic explanation of the disease than with an allergic one.

ENDOCRINE ASPECTS

Besnier [3] considered neurodermatitis to be a "prurigo diathésique" or a "morbid property of the individual." Czerny [4] believed it to be a fundamental disturbance of metabolism, which he called "exudative diathesis." The whole idea of diathesis implies at least a recognition of profound constitutional disturbance rather than a mere clinical classification of cutaneous symptoms. Engman,[11] in 1912 to 1917, studied the possible relationship of thyroid dyscrasias to neurodermatitis. He noticed that in some of his cases there was evidence of mild hypothyroidism and in others there were slight hyperthyroid tendencies. He conceived of a possible cutaneous fraction in the thyroid hormone complex which may affect cornification. Kendall cooperated with Engman in his work at that time and furnished "thyroid B," a by-product obtained in the preparation of thyroxin. Kendall [12] thought his "thyroid B" might have some effect on the skin. Engman used this substance

8. Becker, S. W.: Dermatoses Associated with Neurocirculatory Instability, Arch. Dermat. & Syph. **25**:655 (April) 1932.

9. Stokes, J. H.: Functional Neuroses as Complications of Organic Disease, J. A. M. A. **105**:1007 (Sept. 28) 1935.

10. Peterson, W. F., and Levinson, S. A.: The Skin Reactions, Blood Chemistry and Physical Status of "Normal" Men and of Clinical Patients, Arch. Path. **9**:151 (Jan., pt. 1) 1930.

11. Engman, M. F.: Unpublished data.

12. Kendall, E. C.: Personal communication to Engman.[11]

therapeutically in a number of cases of neurodermatitis, with occasional dramatic success. This work, however, was interrupted by the war, and, since it was never really finished, Engman did not consider the data ready for publication. There was, however, sufficient clinical evidence to warrant further endocrine investigation in neurodermatitis.

MINERAL STUDIES

It seemed to us that all available evidence regarding the pathogenesis of neurodermatitis indicated that patients with this disease suffered from some undiscovered fundamental abnormality of which the cutaneous symptoms were an expression. Since the mineral content of the various body tissues, in particular of the skin, is to a great degree unknown, we decided that a study of the minerals of the skin might throw some light on this problem.

These studies on the mineral content of the skin [13] are reported in detail elsewhere and are the first report of any disease of the skin in which the same biopsy specimens were examined histologically, spectrographically and by microincineration.

Biopsy specimens were obtained from 33 patients with chronic disseminated neurodermatitis, from 83 normal persons and from 55 patients with a variety of cutaneous diseases. Those from the patients with neurodermatitis were taken mostly from the cubital fossa and popliteal regions, where the active lesions were, and from the side of the chest in the midaxillary line, where there never had been any eruption. All of the specimens were treated in the same way in order that the observations would be comparable.

The minerals of these biopsy specimens were studied by microincineration and spectrographic analysis, according to the procedures used by Dr. Gordon H. Scott,[14] of the department of anatomy in Washington University School of Medicine.

One part of each specimen of skin was fixed in an alcohol and solution of formaldehyde mixture, and thin sections were burned on heat-resistant slides in a quartz tube oven at 650 C. By such incineration one removes all organic substances—a troublesome factor in the demonstration of inorganic salts by histochemical technics. Thus the metallic salts of proteins and inorganic substances are reduced to their simplest form for chemical and physical analysis of the total mineral constituents—

13. MacCardle, R. C.; Engman, M. F., Jr., and Engman, M. F.: (*a*) Histology of Neurodermatitis, Arch. Dermat. & Syph. **44**:161 (Aug.) 1941; (*b*) The Spectrographic Analysis of Neurodermatitic Lesions: A Human Magnesium Deficiency, ibid. **44**:429 (Sept.) 1941; (*c*) The Mineral Changes in Neurodermatitis as Revealed by Microincineration, to be published.

14. Scott, G. H.: The Localization of Mineral Salts in Cells of Some Mammalian Tissues by Microincineration, Am. J. Anat. **53**:243, 1933.

those combined with protein molecules and those free as electrolytes—of tissues and cells in the same topographic relationship as existed in the living tissue.

The other half of each biopsy specimen was dissolved in triply distilled mineral-free nitric acid. The resultant "tissue soup" was then dried on a roller carbon and arced before the slit of a quartz spectrograph. Photographic spectrograms were made, and the intensities of lines of radiation for various mineral elements were measured microphotometrically in the physics department of Washington University.

HISTOLOGIC STUDIES

The unaffected skin of patients with neurodermatitis is hyperpigmented and acanthotic. The corneum is hyperkeratotic, and the intercellular fibrils are heavily keratinized. The spinous cells are conspicuously larger than normal spinous cells, and they are usually colored with aniline blue in Masson preparations. Aniline blue is a dye which is adsorbed most readily by collagenic substances, such as are found in the collagenic fibers. Spinous cells of normal skin of normal persons do not become colored with this dye.

In an active lesion, the basal cells are completely depigmented (or fail to form melanin), the chemical constituents (probably proteins) of the spinous cells change physicochemically in such a way that they assume staining properties similar to those of collagenic substances and the corneum is heavily keratinized. Because of the chronologic order in which the perivascular infiltrations of the dermis occur long after the cytoplasmic change appears in the spinous cells, we believe that the primary reaction center ("shock tissue" of Alexander [15]) in this disease is located in the spinous layer or at least in the epidermis.

The healing process evidently involves a slight degree of hyperpigmentation of the basal cells and a change in the staining capacity of the spinous cells. Scarcely any of the spinous cells in a healed lesion will take aniline blue, as do spinous cells in active lesions and in most areas of unaffected skin.

SPECTROGRAPHIC ANALYSIS

The whole skin of patients with neurodermatitis lacks magnesium and usually contains larger amounts of calcium than does skin from normal persons. Unaffected skin from the region of the midaxillary line and skin from active lesions and from healed lesions contain less than half the amount of magnesium found in the skin of normal persons. In other inflammatory diseases of the skin the skin usually contains large

15. Alexander, A.: Zur Histologie des Lichen chronicus Vidal, Dermat. Ztschr. **33**:251, 1921.

amounts of magnesium. In lichen chronicus simplex the cutaneous lesions contain normal amounts of magnesium and in some cases excess amounts of it.

MICROINCINERATION

The content of ash of unaffected skin from patients with neurodermatitis differs from that of skin from normal persons. Most of the spinous cells of such patients' skin contain much less white ash of calcium and magnesium than do normal spinous cells, while the remainder of the spinous cells have much greater amounts of white ash than do most normal spinous cells. It appears that a small number of these spinous cells in the living state must have been overloaded with calcium and magnesium, while the majority of them must either have lost these elements or have been unable to absorb them. This loss and recovery of magnesium and calcium in the spinous cells in the skin of patients with neurodermatitis is probably a fluctuating process that occurs constantly, and an active lesion develops perhaps only when a certain large percentage of spinous cells have lost these elements.

In an active lesion the spinous cells of the epidermis evidently lose both calcium and magnesium, for their cytoplasm contains scarcely any white ash. Nearly all cells of the epidermis, including many of the basal cells, seem to have lost intranuclear silicon. It is difficult to determine whether these ash-poor cells have lost large amounts of their magnesium and calcium or whether they simply have become disorganized to such an extent that they are unable to absorb biologically sufficient amounts of these elements.

In incinerated skin from healed lesions, the large spinous cells are hypermineralized with white ash of calcium and magnesium, and there is silicon present in nearly every nucleus. Evidently the epidermis recovers these elements during the healing process.

COMMENT

The active cutaneous lesion of disseminated neurodermatitis apparently develops in the following manner: The skin is deficient in magnesium. Even the unaffected skin of a patient with neurodermatitis contains less than half the amount of magnesium present in skin from normal persons. The proteins of the spinous cells evidently become reorganized in some way so that they assume staining properties which suggest the presence of collagen-like substances. These altered cells then fail to retain biologically sufficient quantities of calcium and magnesium. Intranuclear silicon either is lost or fails to be absorbed and retained. In fully developed lesions scarcely a single spinous cell possesses even half as much magnesium and calcium as is present in normal skin. Healed lesions, although deficient in magnesium, regain

amounts of spinous cell calcium and possibly some magnesium in excess of quantities found in spinous cells of normal skin. The nuclei of healed lesions recover considerable quantities of silicon.

The skin of patients with neurodermatitis lacks sufficient magnesium but contains plenty of calcium. The relationship between these two elements in skin is exactly the reverse of the normal relationship to begin with, i. e., there is more calcium than magnesium in neurodermatitis skin, while in normal skin there is more magnesium than calcium. Magnesium is essentially a tissue or cellular cation in contrast to calcium, which preponderates in the body fluids and bones.[16] The soft tissues contain more magnesium than calcium. The fragmentary evidence available in the literature.[17] seems to indicate that one effect of magnesium deficiency is a disturbance of normal calcium metabolism.

The loss of intranuclear silicon from epidermal cells during the development of an active lesion and its recovery during the healing process seem to be a unique feature of disseminated neurodermatitis. Silicon is universally present in animal tissues,[18] but its biologic function is unknown. It is usually present in ulcerative lesions, such as those of tuberculosis [18] and the bullous lesions of pemphigus.[18c] In neurodermatitis, however, it is apparently associated with the healing process.

MAGNESIUM DEFICIENCY IN WHITE RATS

Development of Magnesium Deficiency.—Symptoms of magnesium deficiency can be induced experimentally in white rats by feeding them on diets low in magnesium. We have given several groups of rats 21 days old various diets, as indicated in the accompanying table.

Cutaneous lesions and a magnesium deficiency syndrome similar to that described by Kruse, Orent and McCollum [19] in 1931 were obtained in our rats. Not only did extreme redness of the skin develop in these animals, with exudative lesions appearing particularly on the ears and feet, but also hyperirritability. The cutaneous lesions appeared about five to ten days after the beginning of the magnesium-low regimen and continued for about fifteen to twenty days, after which time the lesions

16. Schmidt, C. L. A., and Greenberg, D. M.: Occurrence, Transport and Regulation of Calcium, Magnesium and Phosphorus in the Animal Organism, Physiol. Rev. **15**:297, 1935.

17. Greenberg, D. M.: Mineral Metabolism: Calcium, Magnesium and Phosphorus, in Luck, J. M., and Smith, J. H. C.: Annual Review of Biochemistry, Stanford University, Calif., Annual Reviews, Inc., 1939, vol. 8, p. 269.

18. King, E. J., and Belt, T. H.: The Physiological and Pathological Aspects of Silica, Physiol. Rev. **18**:329, 1938.

19. Kruse, H. D.; Orent, E. R., and McCollum, E. V.: Studies on Magnesium Deficiency in Animals, J. Biol. Chem. **96**:519, 1931.

of the ear healed and did not recur. However, new lesions developed on the back and tail. The rats usually lost weight, and at the age of about 300 days they died.

Histologic Picture of the Cutaneous Lesions.—Histologically, the cutaneous lesions in magnesium-deficient rats are similar to those found in persons with neurodermatitis. The epidermis is acanthotic and hyperkeratotic. The dermis is tightly bound to the epidermis by thickened collagenic fibers that are more numerous and colored more intensely with aniline blue than those of normal rat skin. These changes may be seen both in unaffected skin and in active lesions.

Constituents of Diets Fed to Groups of Rats

	Diet 3	Diet 4	Diet 5	Diet 6	Diet 7
Casein, acid extracted, Gm.	25.00	25.00	25.00	25.00	Purina
Dextrinized corn starch, Gm.	66.12	66.12	66.12	66.12	dog
Dried brewers' yeast, Gm.	2.00	2.00	.....	.....	chow
Vitamin D concentrate 400-D	0.25	0.25	0.25	0.25	
Wheat germ oil, Gm.	1.00	1.00	1.00	1.00	
Sodium chloride, Gm.	0.73	0.73	0.73	0.73	
Potassium chloride, Gm.	1.25	1.25	1.25	1.25	
Ferric phosphate, Gm.	0.12	0.12	0.12	0.12	
Potassium iodide, Gm.	0.03	0.03	0.03	0.03	
Calcium acid phosphate, Gm.	3.00	3.00	3.00	3.00	
Magnesium sulfate, Gm.	0.50	....	0.50	....	
Pantothenic acid, micrograms per 100 Gm.	200.00	200.00	200.00	200.00	
Thiamine hydrochloride, micrograms per 100 Gm.	200.00	200.00	200.00	200.00	
Riboflavin, micrograms per 100 Gm.	300.00	300.00	300.00	300.00	
Nicotinic acid, micrograms per 100 Gm.	200.00	200.00	200.00	200.00	

Add the 80 per cent alcoholic extract of 50 Gm. of ground whole wheat to every hundred grams of stock diet.

Incinerated Lesions of the Skin.—The ash residue of active cutaneous lesions in magnesium-deficient rats differs from that of skin of human beings with neurodermatitis. The spinous cells are heavily loaded with white ash, whereas the spinous cells of neurodermatitis lesions contain little of this ash. The white ash in magnesium-deficient rats is probably calcium, since the spectrograms indicate that little magnesium is present in the skin. As in neurodermatitis lesions, there is little intranuclear silicon to be found in lesions of magnesium-deficient rats.

Parathyroid and Thyroid Glands.—The parathyroid glands are conspicuously enlarged in almost every magnesium-deficient rat after about twenty days of feeding magnesium-low diets. Nearly all of the cells of these glands are at least twice the size of cells in normal parathyroid glands. The cytoplasm is generally filled with small and large vacuoles.

The thyroid gland in a magnesium-deficient rat is demonstrably hyperactive. The follicular epithelium is conspicuously higher and the colloid deposits are smaller than in a normal gland. There are many intrafollicular vacuoles to be found.

The physiologic meaning of this parathyroid hypertrophy is not clear, and conclusions are unjustified. It is significant, however, that many of the soft tissues in such rats are fibrotic and calcified. The kidney tubules generally contain many small deposits of calcium, as Cramer [20] and others have found. Moore, Hallman and Sholl [21] described widespread calcification of soft tissues in calves fed magnesium-low diets. Castleman and Mallory [22] found enlargement and cellular hyperplasia in human hyperparathyroidism that was associated with chronic renal insufficiency. In our rats, after about one hundred and eighty days on magnesium-low diets, the dermis of the skin became thickened and the inguinal canals, which are normally open in males, were generally closed completely or partially by excessive fibrotic growth.

Effects of Anterior Pituitary Extract.—In a few rats on magnesium-deficient diets, daily hypodermic injections of anterior pituitary extract were begun at the time of onset of lesions on the ears. Although these lesions did not heal any more quickly than those in magnesium-deficient controls, the secondary lesions, which in the controls develop on the back and tail after those on the ears heal, did not occur. Other tissue changes, such as enlargement of the parathyroid gland and the pathologic calcification of soft tissues, were as great in the magnesium-deficient rats given injections of anterior pituitary extract as in the controls. The treated animals gained weight largely by accumulation of subcutaneous fat. The thyroid gland appeared normal in most instances, although in some cases there was histologic evidence of hyperactivity.

Comment.—These preliminary experiments in white rats with magnesium deficiency suggest lines for further investigation. The dermatitis in the animals runs a self-limited clinical course, as does neurodermatitis in man. The enlargement of the parathyroids with general calcification and fibrosis apparently indicates a relationship between magnesium and the metabolism of calcium. The occurrence of juvenile cataract in human neurodermatitis may be analogous to the calcium disturbance in magnesium-deficient rats.

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20. Cramer, W.: Experimental Production of Kidney Lesions by Diet, Lancet **2**:174, 1932.

21. Moore, L. A.; Hallman, E. T., and Sholl, L. B.: Cardiovascular and Other Lesions in Calves Fed Diets Low in Magnesium, Arch. Path. **26**:820 (Oct.) 1938.

22. Castleman, B., and Mallory, T. B.: Parathyroid Hyperplasia in Chronic Renal Insufficiency, Am. J. Path. **13**:553, 1937.

SUMMARY

Chronic disseminated neurodermatitis is a well established clinical entity, but as yet no satisfactory explanation of its pathogenesis has been discovered. Atopic or allergic theories have been nebulous and unproved as regards this disease and practical application of allergic regimens of little value. The same may be said for neurogenic theories. In an attempt to throw new light on this problem, biopsy specimens of skin were obtained from both diseased and apparently normal (unaffected) areas. Each specimen was studied in three ways, namely, histologically, spectrographically and by microincineration. Our findings in neurodermatitis were compared with the results of similar studies on skins from normal persons and from patients with a number of other dermatoses.

It was found that chronic disseminated neurodermatitis is characterized by a localized cutaneous magnesium deficiency. Evidently the entire skin of a patient with neurodermatitis lacks sufficient magnesium. The spectrograms of active lesions as well as of unaffected skin and healed lesions from the same patient show low magnesium values. By microincineration it is shown that the spinous cells of an active lesion do not retain calcium or magnesium and that the whole epidermis loses intranuclear silicon. Healed lesions regain calcium in huge quantities, and the intranuclear silicon is recovered.

Histologically, the spinous cells of active lesions change in such a manner that their proteins assume the staining properties of collagenic substances. The basal cells become completely depigmented in active lesions. These changes occur concomitantly with the loss of cytoplasmic calcium and magnesium and of intranuclear silicon. Unaffected skin of patients with neurodermatitis is hyperpigmented and contains much calcium and silicon. Healed lesions, although not heavily pigmented, contain much calcium and silicon. It is believed that the hyperpigmented, magnesium-deficient, unaffected skin of the patients forms a lesion by reason of a physicochemical change in the cytoplasmic proteins of the epidermal cells, which prevents the retention of biologically essential amounts of calcium and silicon.

Lesions similar to those of neurodermatitis have been induced experimentally in rats fed magnesium-low diets. Such animals show extensive metastatic calcification of soft tissues and enlargement of the parathyroid glands. The healing of such induced lesions is not appreciably enhanced by subcutaneous injections of anterior pituitary.

We believe that these studies have revealed factual evidence on which may be built other future investigations. At least a new direction for study has been pointed out that differs from the rather impractical theories at present in vogue.

CONCLUSIONS

1. The present allergic and neurogenic theories of the pathogenesis of chronic disseminated neurodermatitis are unsatisfactory.

2. Histologic, spectrographic and micronincineration studies reveal fundamental differences between the skin of patients with neurodermatitis and that of both normal and pathologic controls. Deficiency in magnesium is most striking.

3. Artificially induced magnesium deficiency in albino rats is accompanied by dermatitis, general calcification of the tissues and parathyroid enlargement.

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PEMPHIGUS

A CLINICAL ANALYSIS AND FOLLOW-UP STUDY OF SIXTY-TWO PATIENTS

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A statistical analysis of clinical records of patients suffering from pemphigus has been undertaken by few authors. Although most authors agree that pemphigus is a serious disease, it is believed by some that it is usually fatal while others hold to the belief that a reasonable number of patients survive.

In order to obtain more complete information about the course of the disease, follow-up studies were carried out on all patients with pemphigus admitted to the Massachusetts General Hospital between the years 1921 and 1936. Of the 63 patients with pemphigus who had come under observation during this period, follow-up data were obtained on all except 1. In this communication the records of the 62 patients who were followed are reviewed. The period was closed in 1936 so that an adequate length of time would have elapsed after the onset of symptoms for observation of the clinical course. Only those patients were selected whose diagnosis was generally agreed on by the members of the dermatologic staff.

REVIEW OF THE LITERATURE

One of the earliest reports in modern literature of a large series of patients with pemphigus was by Kaposi,[1] in 1896. He stated that he had seen more than 300 patients with pemphigus in the wards of the Vienna General Hospital and approximately 100 patients in private practice. It was estimated that approximately 25 per cent of the ward patients had died in the hospital from pemphigus. He thought, however, that this figure was too low, and by comparing the mortality rate among his

This investigation was aided by a grant from the Milton Fund, Harvard University, and the Corn Industries Research Foundation.

From the Dermatological and Medical Clinics of the Massachusetts General Hospital and the Fatigue Laboratory, Harvard University.

1. Kaposi, M.: Ueber den gegenwärtigen Stand der Lehre vom Pemphigus, Arch. f. Dermat. u. Syph. **34**:92, 1896.

private patients, whom he had been following more closely, with that of the ward patients, he estimated that an additional 30 to 40 per cent may have died of the disease after leaving the hospital. Schwimmer,[2] in the same year, reported a mortality rate of 50 per cent for 24 patients under observation in the hospital. None were followed after discharge. Moser [3] reviewed the clinical course of 68 patients. He concluded that the outcome of pemphigus usually is unfavorable because only 18 of the 68 were discharged without lesions. Among the remaining 50 patients the condition of 18 was improved and of 2 unimproved and 20 had died. The condition on discharge of 10 of the patients could not be ascertained by the author from the clinical records. Iser [4] reported on 24 patients with pemphigus. Eighteen were classified as having pemphigus vulgaris. Of these, 6 were discharged as cured, 10 were discharged with the condition improved and 2 had died. There were 3 with pemphigus foliaceus, and all had died. Three patients suffered from pemphigus vegetans. One was discharged as cured; another was discharged with the condition improved, while a third had died. Mierzecki [5] reviewed 80 cases. In his series there were 40 patients with pemphigus vulgaris, 26 (65 per cent) of whom died within two years. There were 30 patients with pemphigus foliaceus, of whom 21 (75 per cent) died within two years. There were 10 patients with pemphigus vegetans, only 2 (20 per cent) of whom died within two years. No follow-up data were collected subsequent to the two year period. The author assumed that some additional deaths might have occurred. Miescher [6] saw 8 patients in Zurich between 1920 and 1927. Four of them with pemphigus vulgaris died. The remaining 4 had pemphigus vegetans; only 1 of these survived, and even this one was not cured. In the discussion of Miescher's paper Ramel mentioned that 11 of his 14 patients with pemphigus had died within a year. Pelagatti [7] reported on 40 patients, of whom 29 (73 per cent) died while in the hospital. Lapowski [8] maintained that all patients with true pemphigus succumb to the disease

2. Schwimmer, in discussion on Kaposi.[1]

3. Moser, K.: Ueber den Pemphigus der Erwachsenen, Inaug. Dissert., Munich, Kastner & Lossen, 1897.

4. Iser, J.: Pemphigusbehandlung, Dermat. Wchnschr. **76**:8, 1923.

5. Mierzecki, H.: Der Pemphigus chronicus in seinen Varietäten als Pemphigus vulgaris, Pemphigus foliaceus und Pemphigus vegetans, Arch. f. Dermat. u. Syph. **162**:115, 1930.

6. Miescher, G., in discussion on Lutz: Pathogenese und die Aetiologie der Pemphigusgruppe, Schweiz. med. Wchnschr. **19**:779, 1938.

7. Pelagatti, M.: Pemfigo. Nota clinica, Ateneo parmense, September 1929, p. 1; abstracted, Dermat. Wchnschr. **91**:1135, 1930.

8. Lapowski, B., in discussion on Peck, S. M.: Pemphigus Treated with Moccasin Venom, Arch. Dermat. & Syph. **33**:151 (Jan.) 1936.

and that if any survive the diagnosis should be questioned. Wile [9] stated that he saw 80 patients with pemphigus during twenty-six years. Of these 100 per cent died within a few months. Gellis and Glass [10] reviewed 170 cases of pemphigus observed at Bellevue Hospital, in New York, between 1911 and 1941. Eighty-five patients (50 per cent) died while in the hospital. By consulting the death certificates filed in New York it was found that 33 additional patients had died of pemphigus outside the hospital, raising the mortality rate to 69.4 per cent, and 4 patients had died of other diseases. Forty-eight patients, however, remained unaccounted for. Eller and Kest [11] reported on 77 patients with pemphigus, of whom 70.1 per cent died while in the hospital.

INCIDENCE

In order to obtain information concerning the incidence of pemphigus, the census of the Massachusetts General Hospital was consulted from 1921 to 1936. During this interval 50,427 new patients (excluding those with syphilis) were admitted to the dermatologic outpatient department, 583,856 new patients were admitted to the entire outpatient department and 117,977 patients were admitted to the wards. Of the 63 patients with pemphigus, 3 were private patients and only 60 were seen in the wards and will be considered in this compilation. On the basis of these figures the frequency of pemphigus at the Massachusetts General Hospital was 1:840 among patients with cutaneous diseases, 1:9,731 among all patients admitted to the outpatient department and 1:1,966 among patients admitted to the wards. It should be appreciated, however, that the Massachusetts General Hospital is one of the few hospitals in New England with a separate dermatologic department. Many patients with unusual cutaneous diseases are referred to the hospital for diagnosis and treatment. Our data on incidence of pemphigus, therefore, are considerably higher than are found in the general population.

CLASSIFICATION AND TREATMENT

Of the 62 patients with pemphigus 38 had diagnoses of pemphigus vulgaris, 14 of pemphigus foliaceus and 10 of pemphigus conjunctivae. No pemphigus vegetans was encountered in this series.

9. Wile, U. J.: Constitutional Background, Differential Diagnosis, and Treatment of Dermatological Lesions About the Eyes, Ears, Nose and Throat, Tr. Am. Acad. Ophth. **43**:43, 1938.

10. Gellis, S., and Glass, F. A.: Pemphigus: A Survey of One Hundred and Seventy Patients Admitted to Bellevue Hospital from 1911 to 1941, Arch. Dermat. & Syph. **44**:321 (Sept.) 1941.

11. Eller, J. J., and Kest, L. H.: Pemphigus: Report of Seventy-Seven Cases, Arch. Dermat. & Syph. **44**:337 (Sept.) 1941.

The type of treatment varied greatly. It included solution of potassium arsenite U. S. P., injections of iron cacodylate and coagulen and injections of mercurochrome. Most patients, however, received only supportive treatment. No consistent correlation between treatment and subsequent clinical course was observed. None of the patients described in this study was treated with adrenal cortex extract or dihydrotachysterol.[12]

Pemphigus Vulgaris.—There were 38 patients with pemphigus vulgaris. The mucous membranes were affected in 26 (68 per cent). All of those with involvement of the mucous membranes had oral lesions. The pharynx was involved in 9 patients, the mucous membranes of the nose in 7, the conjunctivas in 9 and the vaginal mucosa in 2. The cutaneous lesions as well as the lesions of the mucous membrane always healed without scarring.

TABLE 1.—*Comparison of the Various Types of Pemphigus Encountered*

	Number of Cases	Mortality Rate, per Cent	Mucous Membrane Involvement, per Cent	Average Age of Onset, in Years	Percentage of Jews	Sex Incidence, per Cent Males	Eosinophilia, per Cent Eosinophils
Pemphigus vulgaris.....	38	79	68	57	34	50	8
Pemphigus foliaceus.....	14	43	7	38	36	50	11
Combined	52	69	52	50	35	50	9
Pemphigus conjunctivae	10	0	100	61	0	20	3
Total	62	58	60	52	29	45	8

In 13 patients (34 per cent) the mouth was the site of the first lesion. The average interval between the appearance of oral and that of cutaneous lesions was sixteen and six-tenths weeks, the longest interval fifty-two weeks.

The mortality rate among patients with pemphigus vulgaris was 79 per cent. Twenty-six of the 38 patients (68 per cent) died directly from pemphigus, and for 4 additional patients (11 per cent) pemphigus was a contributory cause of death. Of the 30 patients who died directly or indirectly from pemphigus, 25 died within the first year of the disease, 4 within the second year and 1 within the third year. The mortality rate from pemphigus among those with oral lesions was 84 per cent (22 out of 26) and among those without oral lesions 66 per cent (8 out of 12).

12. (*a*) Talbott, J. H.; Lever, W. F., and Consolazio, W. V.: Metabolic Studies on Patients with Pemphigus, J. Invest. Dermat. **3**:31, 1940. (*b*) Lever, W. F., and Talbott, J. H.: Action of Dihydrotachysterol in Chronic Pemphigus, Arch. Dermat. & Syph. **43**:341 (Feb.) 1941.

Four patients (11 per cent) died from diseases not caused by, aggravated by or related to pemphigus. Two of these died from apoplexy, 1 from cancer of the breast and 1 from a gastric hemorrhage. Four patients (11 per cent) are still alive at the time of writing. One of them has been free from lesions for four years. The other 3 have continued to have lesions; in these the disease has lasted fourteen, eleven and six years respectively. Two have a moderate number of lesions, which permits them restricted activity; 1 has been confined to bed because of the persistent development of many bullae.

In addition to the 1 living patient who is free of lesions, 2 of those who died from causes other than pemphigus were free of lesions at the time of death. It is apparent, therefore, that the disease had been arrested in 3 of the 38 patients.

TABLE 2.—*Mortality Rate Among Thirty-Eight Patients with Pemphigus Vulgaris*

	Patients Dead			
	Directly from Pemphigus	Pemphigus Contributory Cause	From Causes Other than Pemphigus	Patients Living
During first year	21	4	1	12
During second year	4	..	2	6
During third year	1	..	..	5
During fourth year	....	..	..	5
During fifth year	....	..	..	5
After fifth year	....	..	1	....
Total	26	4	4	4
Average duration of disease	7.7 months	5.3 months	26.5 months	9 years

Whenever a remission occurs in a patient with pemphigus vulgaris the question arises whether the remission will be temporary or permanent. Of the 38 patients with pemphigus vulgaris 4 showed complete clearing and 5 considerable improvement at one stage. Of the 4 patients whose disease cleared completely, 3 remained well, while 1 had a relapse; this patient is still alive. Of the 5 patients in whom decided improvement occurred, 4 remained improved and 1 had a relapse and died of pemphigus. In summary, complete clearing or great improvement occurred in 9 out of 38 patients, was permanent in 7 and was followed by a relapse in only 2.

The age of onset varied between 29 and 85, the average being 57. There were 19 men and 19 women. Moderate eosinophilia was frequently observed. The average maximum eosinophil count was 8 per cent. Only a few chemical determinations on the blood were made in this series of patients. This subject has been discussed in a recent communication from our laboratory.[12a]

Of interest is the high frequency of pemphigus vulgaris in Jews, its occurrence at an earlier age, its tendency to start with oral lesions and its greater mortality rate. Thirteen of the 38 patients (34 per cent) were Jews. Among the Jewish patients only 1 (8 per cent) was over 60 years of age at the onset of the disease, while among the gentiles 13 (52 per cent) were over 60; hence the average age of onset was 49 for the Jewish patients and 61 for the non-Jewish patients. The disease had its first manifestation in the mouth in 62 per cent of the Jews but in only 20 per cent of the gentiles. The mortality rate among the Jews was 100 per cent and among the gentiles 68 per cent.

TABLE 3.—*Comparison of Age and Mortality Rate Among Jews and Gentiles with Pemphigus Vulgaris*

		Gentiles (25)		
Age	Jews (13) Death Due to Pemphigus	Death Due to Pemphigus	Death from Causes Other than Pemphigus	Living
25-30	1	1		
31-35	1			
36-40	1	1		
41-45	3	1		
46-50	1	1	..	1
51-55	3	2	..	1
56-60	2	3	..	1
61-65	..	..	1	
66-70	..	2	2	1
71-75	..	3		
76-80	1	3		
81-85	..	..	1	
Onset later than 60	1 (8%)	13 (52%)		
Deaths	13 (100%)	17 (68%)		

Pemphigus Foliaceus.—Fourteen of the patients (22 per cent) suffered from pemphigus foliaceus. In all patients the first manifestations were on the skin. The mucous membranes of the mouth were affected in only 1 patient (7 per cent), who showed a few transient lesions in his mouth. The palpebral conjunctivas were affected in 5 of the 14 (36 per cent). The conjunctivas of these patients were red and swollen and often had a profuse, purulent discharge. However, scarring did not take place, and the corneas were never affected. Involvement of the throat, nose and vagina was never noted.

Pemphigus foliaceus often arose in young adult persons. Eight of the 14 patients (57 per cent) were 30 years of age or younger at the onset of the disease. The average age of onset was 38.

Six patients died from pemphigus foliaceus, a mortality rate of 43 per cent. Three of these 6 died in the first year of illness, 2 in the second

and 1 in the third. Three others (21 per cent) died from causes other than pemphigus: The death of 1 was due to a gastric hemorrhage and that of another to an embolus dislodged from a stenosed mitral valve, and a third committed suicide. Five patients (36 per cent) are alive at the time of writing. The mortality rate was lowest in the young patients. Of the 8 patients in whom the disease started at the age of 30 or less, only 1 (12 per cent) died of pemphigus, 2 died of diseases not related to pemphigus and 5 are living.

In the 5 living patients the disease has been active for twenty-two, twenty-one, seventeen, eleven and six years, respectively, an average of fifteen years. This demonstrates that pemphigus foliaceus may be a chronic disease and that the chance for survival for younger patients is good. Two have improved sufficiently to permit restricted activity; the remaining 3 are in bad condition. Their skin remains tender, and the

TABLE 4.—*Mortality Rate Among Fourteen Patients with Pemphigus Foliaceus*

	Patients Dead		
	Directly from Pemphigus	From Causes Other than Pemphigus	Patients Living
During first year	3	..	11
During second year	2	..	9
During third year	1	..	8
During fourth year	..	1	7
During fifth year	..	..	7
After fifth year	..	2	....
Total	6	3	5
Average duration of disease	14.7 months	5.7 years	15.4 years

clothing adheres to the skin because of the persistent oozing, so that loose garments only are comfortable. Large amounts of scales are shed, and itching is severe.

The patients were equally divided as to sex. An eosinophilia was characteristic. The average of the maximum eosinophil counts was 11 per cent, and the highest was 26 per cent.

Five of the 15 patients (36 per cent) were Jews. In contrast to pemphigus vulgaris, with which type all the Jewish patients died, 2 of them with pemphigus foliaceus are living at present.

Pemphigus Conjunctivae.—Ten patients (16 per cent) were affected with this form of pemphigus. In addition to the ocular involvement, 9 patients had lesions on other mucous membranes, and 5 had cutaneous lesions. The disease began on the mucous membranes in 7 of the 10 patients, on the skin in 2 and simultaneously on the skin and mucous membranes in 1.

The inflammation of the conjunctiva was bilateral in 9 patients and unilateral in 1 and always resulted in scar formation and synechiae. Actual vesicle formation on the conjunctiva, which according to Duke-Elder [13] has been observed in one fourth of the cases in the literature, was seen in 1 patient. Involvement of the cornea occurred in 6 patients (60 per cent), in both eyes in 4 and in one eye in 2. Owing to the severity of the corneal involvement, 3 of the patients became, for practical purposes, blind in both eyes, and a fourth patient became practically blind in one eye. The perforation of the right cornea in 1 of these patients led to panophthalmitis and necessitated the evisceration of the bulbus.

All but 1 of the 10 patients had lesions on mucous membranes besides those of the eye. In contrast with the conjunctival lesions, those of the

TABLE 5.—*Distribution of Lesions in the Ten Patients with Pemphigus Conjunctivae*

Patient	Mucous Membranes				Skin
	Eyes	Mouth	Esophagus	Nose	
1	+ *	—	....	....	+
2	+	—	....	....	....
3	+	—	+	—	....
4	+	+	....	....	....
5	+	—	+	....	—
6	+	+	+	....	+
7	+	—	....	....	....
8	+	+	+	....	—
9	+	—	....	....	—
10	+	....	....	....	....

* —, indicates lesions leaving no scars; +, lesions leaving scars.

mucous membranes of the nose, throat, mouth, esophagus or vagina did not always heal with scarring. In only 6 patients was scar formation observed in regions other than the eye. Lesions in the mouth were observed in 9 patients, resulting in scars in 3. While blisters are only rarely encountered on the conjunctiva, they are usually present at one time or other on the mucous membranes of the mouth. Usually there were relatively few active lesions at one time, and mastication and swallowing were never sufficiently painful to prevent an adequate intake of food. The vermilion border of the lips, to which the oral lesions of pemphigus vulgaris often spread, was never involved. The destruction in the mouth due to scarring may be severe, as, for example, in a patient whose soft palate was virtually adherent to the posterior pharyngeal wall leaving only a negligible opening between the upper and lower

13. Duke-Elder, W. S.: Textbook of Ophthalmology, St. Louis, C. V. Mosby Company, 1938, vol. 2, p. 1728.

parts of the pharynx. Involvement of the esophagus was observed in 4 of our patients and caused stenosis of a more or less severe degree. One of the patients died of inanition and general debility due to complete stenosis of the esophagus. Another patient was compelled to visit the hospital at regular intervals for dilatation of the stricture.

According to Knapp,[14] cutaneous lesions are present in three fourths of the cases. In this series the skin was involved in 5 patients (50 per cent). The cutaneous eruption was always limited to a few areas, and the general health was never affected. In 3 of the patients the cutaneous lesions were present for only a few months and did not recur in spite of continued activity of the mucosal lesions. In 2 patients, however, scars formed in some of the cutaneous lesions. This must be regarded as an unusual occurrence, as only 5 instances of scar formation on the skin in pemphigus conjunctivae have been reported in the literature, namely, by Morris and Roberts,[15] Ramel,[16] Meyer,[17] Klauder [18] and O'Leary and Goeckerman.[19] For this reason, these 2 cases are being reported separately in greater detail.[20]

That pemphigus conjunctivae is a chronic and benign disease is evident in our 10 patients. In 8 of them the disease remained active either until their death or up to the present, an average of seven and five-tenths years. In the other 2 the disease became arrested after many years' duration. None of the patients was seriously ill from pemphigus at any time, and none died of it. However, the complications may be serious, as in the case of a patient who, as mentioned before, died from inanition and general debility due to complete stenosis of the esophagus. Of the other 9 patients, 7 are still alive, 1 died of a cerebral thrombosis following prostatectomy and 1 died of "old age," at the age of 84.

The age of onset varied between 47 and 70; the average was 61. Pemphigus of the conjunctiva seems therefore to be a disease of advanced

14. Knapp, A.: Medical Ophthalmology, Philadelphia, P. Blakiston's Son & Co., 1918, p. 453.

15. Morris, M., and Roberts, H. L.: Pemphigus of the Skin and Mucous Membranes of the Mouth, Associated with "Essential Shrinking" and Pemphigus of the Conjunctivae, Brit. J. Dermat. **1**:175, 1889.

16. Ramel, E.: Sur une dermatose voisine du pemphigus à évolution cicatricielle, essentielle, Ann. de dermat. et syph. **5**:403, 1924.

17. Meyer, F. W.: Essentielle Bindehautschrumpfung oder Pemphigus conjunctivae, Klin. Monatsbl. f. Augenh. **101**:708, 1938.

18. Klauder, J. V.: Argyria, Lupus Erythematosus of the Scalp: Essential Shriveling of the Conjunctivae (Ocular Pemphigus), with Ocular, Oral and Vulvar Lesions, Arch. Dermat. & Syph. **37**:687 (April) 1938.

19. O'Leary, P. A., and Goeckerman, W. H.: Chronic Lupus Erythematosus Disseminatus (Lupus Erythematosus—Pemphigus Syndrome of Ormsby and Senear), Arch. Dermat. & Syph. **15**:92 (Jan.) 1927.

20. Lever, W. F.: Pemphigus Conjunctivae with Scarring of the Skin: Report of Three Cases, to be published.

age. Eight patients were women, and 2 were men. The eosinophil count was generally normal, and the average maximum count was 3.3 per cent.

None of the patients was Jewish. This is in noteworthy contrast to pemphigus vulgaris and pemphigus foliaceus; more than one third of the patients wtih these diseases were Jews.

SUMMARY

A clinical report and a follow-up study of 62 patients suffering from pemphigus are presented. The patients were admitted to the Massachusetts General Hospital between 1921 and 1936. Adequate follow-up observations have been gathered either to the present time if the patient is still alive or to the time of death.

There were 38 patients with pemphigus vulgaris, 14 with pemphigus foliaceus and 10 with pemphigus conjunctivae.

Pemphigus vulgaris and pemphigus conjunctivae tended to appear at an advanced age, on the average at 57 and 61 years of age respectively, while pemphigus foliaceus started commonly at an early adult age, on the average at 38 years of age.

Oral lesions were present in the majority of patients with pemphigus vulgaris (68 per cent) and pemphigus conjunctivae (90 per cent), but only 1 patient (7 per cent) with pemphigus foliaceus showed a few transient oral lesions. In pemphigus vulgaris the mortality rate for patients with oral lesions was 84 per cent and for those without oral lesions 66 per cent.

The mortality rate among patients with pemphigus vulgaris was 79 per cent, among those with pemphigus foliaceus 43 per cent and among those with pemphigus conjunctivae 0. Of those who died of pemphigus vulgaris, 83 per cent had died at the end of the first year and 97 per cent at the end of the second year. Of those who died of pemphigus foliaceus, 50 per cent died within the first year and 83 per cent within the first two years.

Of interest is the racial distribution: Thirty-four per cent of the patients with pemphigus vulgaris and 36 per cent of the patients with pemphigus foliaceus were Jews, but none of the patients with pemphigus conjunctivae was a Jew. In a comparison of the group of Jewish patients with the group of non-Jewish patients suffering from pemphigus vulgaris, it became apparent that pemphigus vulgaris on the average started earlier in the Jews, of whom only 8 per cent were over 60 years of age at the time of onset, as compared with 52 per cent of the non-Jewish patients. Furthermore, pemphigus vulgaris started more frequently in the mouth in the Jews, in 62 per cent, as compared with 20 per cent of the non-Jewish patients. The mortality rate of pemphigus vulgaris was 100 per cent among the Jews and 68 per cent among the gentiles.

KERATOCONUS ASSOCIATED WITH ATOPIC DERMATITIS

REPORT OF TWO CASES

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Cataract associated with atopic dermatitis (disseminated neurodermatitis) has been reported fairly frequently, particularly in the recent literature. According to Tostevin,[1] Rothmund was the first to describe this occurrence. Cataract in association with this disease of the skin has been reported by a number of other European authors (for a summary, see Ollendorf and Levy[2]). The first case reported in the American literature was that of W. T. Davis[3] in 1921. Since then, many others have been recorded all over the world (Sulzberger,[4] Brunsting,[5] Daniel,[6] Tostevin,[1] Cazort and Cook,[7] Winkler,[8] Rollin,[9]

From the Dermatologic Department of Montefiore Hospital for Chronic Diseases (service of Dr. Fred Wise), New York.

1. Tostevin, A. L.: Cataract with Neurodermatitis Chronica, M. J. Australia **2**:647, 1938.

2. Ollendorf, H., and Levy, G.: Neurodermatitis und Katarakt, Arch. f. Dermat. u. Syph. **164**:683, 1932.

3. Davis, W. T.: The Relation of the Eye and Certain Skin Diseases, South. M. J. **14**:237, 1921.

4. Sulzberger, M. B.: Atopic Dermatitis with Cataract, Arch. Dermat. & Syph. **34**:328 (Aug.) 1936; Atopic Dermatitis with Unilateral Cataract, ibid. **35**:368 (Feb.) 1937.

5. Brunsting, L. A.: Atopic Dermatitis of Young Adults: Analysis of Precipitating Factors in One Hundred and One Cases and Report of Ten Cases with Associated Juvenile Cataracts, Arch. Dermat. & Syph. **34**:935 (Dec.) 1936.

6. Daniel, R. K.: Allergy and Cataracts, J. A. M. A. **105**:481 (Aug. 17) 1935.

7. Cazort, A. G., and Cook, C. C.: Atopic Dermatitis with Rapidly Maturing Cataracts, J. Allergy **9**:521, 1938.

8. Winkler, A.: Beitrag zur Genese der Cataracta dermatogens, Arch. f. Ophth. **139**:526, 1938.

9. Rollin, J. L.: Katarakt bei Neurodermie, Ztschr. f. Augenh. **92**:16, 1937.

and Ollendorf and Levy [2]). Another ocular complication of atopic dermatitis was reported by Pillat [10] in 1937 under the name of keratitis superficialis punctata.

During the past year we have had the opportunity to observe several cases of cataract associated with atopic dermatitis as well as 2 cases of atopic dermatitis of many years' duration associated with bilateral keratoconus (conical cornea). A careful survey of the literature disclosed only 1 report of keratoconus as a complication of atopic dermatitis (Hilgartner, Hilgartner and Gilbert [11]). We feel that in our 2 cases the keratoconus may in some way be intimately associated with atopic dermatitis, although the possibility of a coincidence cannot be excluded.

REPORT OF CASES

CASE 1.—C. T., a white woman aged 30, was admitted to the ophthalmologic service because of visual changes of fourteen years' duration. These changes began in the left eye at the age of 16 and were followed by sudden blindness in the left eye at the age of 21. Since the age of 3 months the patient has suffered from atopic dermatitis, with remissions and exacerbations. Her mother had asthma.

On admission a physical examination showed the following picture: The skin was greatly thickened, lichenified and pigmented on the entire body, particularly on the face and chest. Small scattered papules were seen in many different areas. The ophthalmologic report (Dr. B. S. Kramer) stated that there were lenticular opacities of both eyes and corneal opacities of the right eye. The pupils were unequal, the left one being larger than the right. Both pupils were ovoid and reacted to light. The anterior chambers were deep, and there was a bilateral keratoconus. High myopia was also present. Scratch tests disclosed a 4 plus reaction to eight food and inhalant allergens.

Examination of the blood showed 14,000 white blood cells per cubic millimeter, with 13 per cent eosinophils. The results of the rest of the blood count, urinalysis and chemical and serologic examinations of the blood were normal.

Local treatment of her skin and changes in her glasses were carried out, with some improvement.

CASE 2.—I. G., a white woman aged 24, was admitted to the dermatologic service in 1937 for generalized atopic dermatitis, from which she had suffered since the age of 9 years and which was associated with severe bronchial asthma. Eggs, milk, flowers and wheat caused sneezing and asthma. Urticaria developed when the patient wore articles containing silk. Intradermal tests performed at another hospital showed positive reactions to ten food and inhalant allergens. There was a vague history of progressive loss of vision for from eight to ten years in both eyes.

Examination disclosed a dry, scaly scalp, alopecia areata and canities in patches. The face was erythematous, scaly and lichenified; the skin of the neck was lichenified

10. Pillat, A.: Zur Mitbeteiligung der Hornhaut beim Ekzem, Wien. klin. Wchnschr. **50**:768, 1937.

11. Hilgartner, H. L.; Hilgartner, H. L., Jr., and Gilbert, J. T.: Keratoconus Successfully Treated with Organotherapy, Radium and Shortwave Diathermy, Am. J. Ophth. **20**:1032, 1937.

and excoriated, and the upper portion of the chest was erythematous, lichenified and excoriated. There was some edema of the nipples. The skin of the arms and legs was lichenified, particularly in the cubital and popliteal spaces. There was a generalized brownish pigmentation. Wheezing, rales in the chest and a hepatosplenomegaly were also present. The ophthalmologist (Dr. B. S. Kramer) reported bilateral keratoconus and corneal opacities.

The basal metabolic rate was + 19 per cent. An electrocardiogram showed sinus tachycardia and right axis deviation. The results of chemical and serologic examinations of the blood were normal. The differential blood cell count showed 21 per cent eosinophils. The patient during four years of observation was treated both for asthma and for atopic dermatitis by all types of known therapy, with little improvement. While in the hospital, she had two attacks of bronchopneumonia and a pulmonary abscess. Her asthma became so severe that she was finally sent to the Southwest. Scratch tests revealed a 4 plus reaction to thirty-three food and inhalant allergens.

During her stay in the hospital, both contact lenses and telescopic lenses were tried, with a slight degree of success.

COMMENT

In both these cases the atopic dermatitis was severe and of many years' duration, as were the ocular changes. In case 1 there were a family history of atopy, multiple positive reactions by scratch tests to inhalants and foods and eosinophilia. The keratoconus was of eleven years' duration and was associated with myopia.

In case 2 there were long-standing visual difficulty, multiple positive reactions to scratch tests with inhalants and foods, severe bronchial asthma and eosinophilia, in addition to the atopic dermatitis.

In both cases the cutaneous changes were almost universal, especially in case 2, and the same lichenified, pigmented and scaly appearance was noted. The facial appearance of the 2 patients was similar because of the changes in the skin and the dull stare of the eyes.

The detailed ophthalmologic reports are omitted, because they will be the subject of a separate communication. However, it would not be amiss to state that according to Gifford,[12] keratoconus or conical cornea is a corneal degeneration beginning about the tenth year of life, running a typical course of progression and then at a certain point becoming stationary. The cause is unknown, although heredity plays a role in some cases. The central part of the cornea becomes thin, and the intraocular tension forces the cornea into its conical shape. Reduced vision, myopia and myopic astigmatism are present. Both eyes are usually involved.

We believe that the ocular changes reported in our cases are an exceedingly rare complication of atopic dermatitis, since we were able

12. Gifford, S. R.: A Textbook of Ophthalmology, Philadelphia, W. B. Saunders Company, 1938, pp. 201 and 202.

to find only 1 similar case reported in the literature.[11] However, since atopic dermatitis is a rather common disease of the skin, it is possible that the association in our 2 cases with keratoconus might have been purely coincidental.

SUMMARY

We present 2 cases of atopic dermatitis associated with keratoconus (conical cornea). It is suggested that keratoconus may be a hitherto not recognized ocular complication of atopic dermatitis.

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DISSEMINATED LUPUS ERYTHEMATOSUS

REPORT OF TWO CASES WITH UNUSUAL CLINICAL MANIFESTATIONS

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There have been numerous recent articles devoted to the clinical and pathologic manifestations of disseminated lupus erythematosus. This is a report of 2 cases of acute disseminated erythematosus with certain unusual features which were suggestive of adrenal insufficiency. The postmortem examination in 1 case is described.

REPORT OF CASES

CASE 1.—*Clinical History.*—E. L., a 35 year old white housewife, was admitted to the Boston City Hospital on April 4, 1940 and died on July 9. The patient's past history and family history were not relevant. The earliest symptoms referable to her present illness appeared after the delivery of her first child in December 1933. With this pregnancy she was said to have had a toxemia. Three months post partum there developed stiffness and swelling of the hands and fleeting pains in the back. After these symptoms had persisted several months she consulted a physician, who found definite swelling of the hands, with some enlargement around the phalangeal joints. The blood pressure at this time was 140 mm. of mercury systolic and 90 mm. diastolic. The hemoglobin content of the blood was 60 per cent. No abnormal urinary findings were observed.

The patient continued to feel "run down" during the next two years. She was then asymptomatic until March 1938, during the latter part of her second pregnancy. At this time her hands again became swollen, but there were no pains in the joints. Several determinations of blood pressure prior to delivery varied between 178 systolic and 100 diastolic and 126 systolic and 58 diastolic. Following delivery in April 1938 she made an uneventful symptomatic recovery.

In January 1939 pain developed in the muscles and joints, especially in the legs. These symptoms persisted intermittently until her admission to the hospital and were accompanied by a progressive loss of strength and a slight loss of weight. During the summer of 1939, following repeated sunburn, the exposed areas of the skin became dark. The patient and her family noted that this pigmentation persisted unchanged during the next nine months. In February 1940 the patient was examined in another hospital, and a diagnosis of chronic rheumatoid arthritis was made. Laboratory data at this time included a hemoglobin content of 82 per cent, an erythrocyte count of 4,140,000, a leukocyte count of 5,750 and a normal differential count. The sedimentation rate of the blood was elevated. On April 4 the patient was admitted to the Boston City Hospital. In the two weeks preceding this date there had been chills, fever and a persistent cough productive of yellow sputum.

From the Mallory Institute of Pathology, Boston City Hospital, Boston.

Physical Examination on Admission.—The patient was a well developed, slightly obese white woman who did not appear acutely ill. The skin exhibited a diffuse light brown pigmentation, which was least conspicuous on the trunk, where there were small mottled brown areas suggesting freckles. There was no pigmentation of the mucous membranes. In the axillas and in the right inguinal region the lymph nodes were slightly enlarged and slightly tender. The eye grounds appeared normal. The heart was normal. The blood pressure was 160 systolic and 105 diastolic. There was dulness over the base of the left lung posteriorly, and a few moist rales were heard at the base of each lung posteriorly. The liver and spleen were not palpable. There were fusiform swelling and limitation of motion of the fingers but no ankylosis. Other joints were normal. On pelvic examination a moderate periurethritis was observed.

Roentgen Ray Examination.—Roentgenograms of the chest showed mottled areas of increased density at the base of the left lung. Examination of the hands showed a punched-out lesion at the distal end of the right third metacarpal bone. No deformities could be demonstrated in roentgenograms of the shoulders, pelvis, spine and feet.

Laboratory Data.—The urine on repeated examinations contained traces of albumin, many leukocytes, occasional erythrocytes and rare granular casts. The specific gravity after a concentration test was 1.018. After injection of phenolsulfonphthalein intravenously, 35 per cent of the dye was excreted within fifteen minutes and 93 per cent within two hours. Escherichia coli was recovered from cultures of the urine on many occasions.

Examination of the blood showed 3,700,000 erythrocytes per cubic millimeter and a hemoglobin content of 71 per cent (Sahli). Subsequently a progressive normocytic, normochromic anemia ensued, so that the initial levels were maintained only by the administration of several blood transfusions. The leukocytes varied between 2,500 and 4,400 per cubic millimeter. The differential leukocyte counts were normal.

There was no growth of bacteria in seven blood cultures. An agglutination test for Brucella was negative. The Hinton and Kahn reactions of the blood were negative. The Wassermann reaction of the blood was anticomplementary. The reaction to a gonococcus complement fixation test of the serum was positive on three occasions. The corrected sedimentation rates of the blood were decidedly elevated. Examination of the stools showed no abnormalities. Electrocardiograms showed low voltage but were otherwise normal.

The nonprotein nitrogen content of the plasma was 30 mg. per hundred cubic centimeters on admission. The total protein content of the blood plasma was 5 Gm. per hundred cubic centimeters (2.1 Gm. of albumin and 2.9 Gm. of globulin). One fasting blood sugar level was 90 mg. per hundred cubic centimeters. The serum calcium content was 8.3 mg. and the serum phosphorus 3.1 mg. per hundred cubic centimeters. Further chemical determinations on the blood are discussed in another part of this paper.

Course of Illness.—The temperature fluctuated between 98 and 104 F. and varied about 3 degrees daily. There were several afebrile periods of three to four days. Terminally the temperature was 106 F. The pulse rate varied between 80 and 100 and the respiratory rate between 20 and 30.

During the first six weeks the patient lost weight and strength. There were diffuse abdominal pain, nausea and occasional vomiting. The blood pressure fell from 160 systolic and 105 diastolic to 95 systolic and 60 diastolic. The pigmentation of the skin became more intense. On June 5, in the beginning of the seventh

hospital week, a symmetric, macular, scaly, erythematous rash appeared on the eyebrows and over the bridge of the nose. A few days later purple slightly raised discrete lesions were observed on the tips of the fingers and crusted erythematous lesions developed on the ears. Slight alopecia of the eyebrows was now apparent. The cutaneous lesions gradually subsided and were scarcely visible at the time of death.

From the time of onset of the rash to the time of death, approximately four weeks later, the major complaints were anorexia, nausea, vomiting and severe abdominal pain. A determination of serum sodium early in this period revealed 126 milliequivalents per liter. Large amounts of sodium chloride and sodium citrate were administered intravenously. In addition, the patient recevied daily subcutaneous injections of 5 or 10 mg. of desoxycorticosterone acetate. With these measures the patient appeared to improve, although the nausea and vomiting persisted and there was no gain in weight. The blood pressure rose to 120 systolic and 80 diastolic. The determinations of serum sodium returned to a normal level. Several determinations of serum potassium and of blood chlorides during this period of intensive therapy were normal. The determinations of nonprotein nitrogen in the plasma varied between 30 and 65 mg. per hundred cubic centimeters.

During the terminal four weeks of the illness the patient's skin became deeply bronzed. There was progressive asthenia. Three days before death, during the eleventh hospital week and coincident with extremely hot weather, the patient's temperature rose and a coarse tremor of the hands appeared. Large quantities of parenteral fluids and increased amounts of desoxycorticosterone acetate (10 to 20 mg. daily) were given. She did not respond to these measures and died on July 9. The serum sodium content on the day of death was 141.6 milliequivalents per liter.

Autopsy.—Postmortem examination was performed two hours after death. The gross anatomic diagnoses were as follows: acute pyelonephritis, bilateral; acute ureteritis and cystitis; calcified tuberculous lymph nodes, tracheobronchial and periportal; fibrous pleuritis, bilateral; slight hydropericardium; generalized pigmentation of the skin, and emaciation.

Gross Examination: The body was that of a normally developed, poorly nourished woman. The skin of the entire body showed a light brown pigmentation, which was most pronounced about the mouth and on the neck. There was a general depletion of body fat. The persisting fat was orange. The peritoneal cavity contained approximately 75 cc. of clear pale yellow fluid. The spleen was attached to the lateral abdominal wall by many thin fibrous bands. The peritoneal surfaces were gray and glistening. In the gastrohepatic ligament there were scattered, moderately enlarged lymph nodes, many of which were calcified.

Both pleural cavities were completely obliterated by multiple firm fibrous adhesions. The pericardial sac was moderately distended and contained approximately 75 cc. of clear yellow fluid. The pericardial surfaces were smooth, glistening and without adhesions. The heart was of normal size, weighing 300 Gm. No gross abnormalities were noted in the myocardium, endocardium, valves or coronary vessels. The lungs were soft, crepitant and not increased in weight. About the trachea and main bronchi were moderately enlarged calcified lymph nodes.

The spleen was enlarged, weighing 380 Gm. The pulp was purplish red and soft. The liver was of average size, weighing 1,520 Gm. Its external and cut surfaces appeared normal. The biliary tract, pancreas and entire gastrointestinal tract were not remarkable. The kidneys, which were large, had a combined weight of 420 Gm. and were essentially similar in size and appearance. The capsules stripped with difficulty to expose a finely granular, light brown external surface

on which were scattered small dark red petechiae varying from 1 to 2 mm. in diameter. Also, on the outer surface of each kidney were scattered, irregularly round, mottled gray and red, slightly elevated areas which varied from 0.5 to 1.5 cm. in diameter. Occasional small pitted depressions were seen. The cut surfaces disclosed a light brown cortex which was well delimited from the pyramids. Underlying the raised areas on the external surfaces were dull red, roughly wedge-shaped areas extending downward from the surface into the peripheral portions of the pyramids. The mucosal surfaces of the renal calixes, pelves, ureters and bladder were grayish red and roughened.

Both adrenals were of average size and configuration. On cut section the cortices appeared paler than usual. No other abnormalities were noted.

The genitalia, vertebral bone marrow, thyroid, meninges and brain were not remarkable.

Microscopic Examination: Three sections of the heart were examined. Two were from the left ventricular wall and one from the interventricular septum. In the pericardium scattered newly formed capillaries were present. The epicardial branches of the coronary arteries showed fibrous intimal thickening. In the myocardium were occasional single necrotic muscle fibers which were infiltrated with mononuclear macrophages. The interstitial tissue of the myocardium contained focal collections of varying numbers of lymphocytes, plasma cells, polymorphonuclear leukocytes and macrophages. Some of the macrophages were large with an abundant pink-staining cytoplasm. A few of them contained more than one nucleus. No abnormalities were present in the endocardium of these sections.

There were no significant microscopic lesions in the lungs. The pleura was thickened and consisted of loose vascular connective tissue infiltrated with a few macrophages.

The malpighian corpuscles of the spleen were diminished in size. The trabeculae were infiltrated with plasma cells. About the small arterioles were thick concentric layers of hyaline material.

Focal sparse collections of polymorphonuclear leukocytes were present in the interstitial connective tissue of the pancreas, which was otherwise not abnormal. The liver cord cells in the portal areas contained large and small fat droplets. No focal necrosis of the liver cells and no hemosiderosis was present.

Many sections of the kidneys were examined. The most striking changes were observed in the glomeruli. Almost every glomerulus was enlarged, ischemic and more cellular than usual. The increase in cells in the glomeruli was presumably due to a proliferation of endothelial cells. With oxidase stains there were a certain number of oxidase-positive mononuclear cells in the tufts, but the great majority of the cells were oxidase negative. With the Lee-Brown modification of Mallory's aniline blue stain the glomerular basement membranes showed a focal irregular thickening. With this same stain intracapillary fibers were seen in focal areas. Associated with these fibers were increased numbers of endothelial cells. In many glomeruli there were areas where the epithelial cells of the tufts were swollen and sometimes vacuolated. These swollen cells contained no fat, but occasionally hyaline droplets were seen in the cytoplasm. In addition there were, in many instances, foci of necrosis in the glomerular tufts. These necrotic areas contained polymorphonuclear leukocytes and sometimes fibrin. In several glomeruli such necrosis involved the external wall of the peripheral capillaries of the tuft with deposition of fibrin and swelling of the overlying epithelial cells. There were occasional adhesions between capsule and tuft and occasional crescents.

The changes in the tubules were less decided. A few of the tubular lumens contained red blood cells, and a certain number contained hemoglobin casts. In scattered areas there was necrosis of the tubular cells. A few tubular epithelial cells were vacuolated. With the scarlet red stain no fat could be demonstrated in the tubular cells. In the interstitial tissue there were focal collections of plasma cells. The arterioles and arteries showed no significant changes.

Certain sections of kidney were taken to include portions of the dark red areas which were observed grossly in the cortices. These sections showed destruction and disappearance of most of the tubules. The interstitial tissue was heavily infiltrated with polymorphonuclear leukocytes and lymphocytes. Similar cells were present in the lumens of many of the remaining tubules. A few of the tubules contained clumps of bacilli. The capillaries and venules in and about the areas of inflammation were congested. The mucosal surface of the renal pelvis was intact. The peripelvic connective tissue showed focal infiltration with lymphocytes and occasional polymorphonuclear leukocytes.

Multiple sections from both adrenal glands revealed that the usual architecture was preserved. No necrotic cells were observed. There was a great depletion in the amount of lipid in the cortical cells, as indicated by stains for fat.

Sections of vertebral marrow showed normal erythropoiesis and myelopoiesis.

A section of skin removed from the abdominal wall showed a slight brown granular pigmentation of the basal epithelial layer. No iron pigment was present.

Sections of the parathyroid, thyroid and pituitary glands showed no abnormalities. In the ovaries there were many primordial follicles and one developing graafian follicle.

Several sections of cerebral cortex showed no changes. A section from the right mamillary body contained focal round or irregularly shaped areas of recent hemorrhage about which was a slight glial proliferation.

A section of one periportal lymph node showed an infarct-like necrosis of the entire pulp. The architecture was preserved, but the pulp cells showed evidence of degeneration, as indicated by the blurring of the nuclear outlines. In many areas no nuclear portions could be identified. Scattered, irregularly shaped clumps of degenerating fibrin were present in the pulp. About this necrotic pulp was a dense fibrous capsule the inner layer of which showed a moderate infiltration with lymphocytes, plasma cells, eosinophilic polymorphonuclear leukocytes and mononuclear macrophages. No giant cells were present. A stain for tubercle bacilli was negative.

Another periportal lymph node consisted mainly of a large, irregularly shaped mass of partially calcified acellular hyaline substance. At the periphery of this node, there were several round islands of lymphatic tissue in which were focal areas of necrosis with disappearance of many and fragmentation of the remaining nuclei.

Several hilar lymph nodes consisted of central calcified hyaline masses with peripheral lymphoid tissue containing anthrocotic pigment. No focal areas of necrosis of lymphoid tissue were observed in these lymph nodes.

A postmortem culture of the heart's blood and of the spleen yielded no growth. Esch. coli was recovered from a swab inserted into the renal parenchyma.

Diagnosis: To the gross anatomic diagnoses the following microscopic diagnoses were appended: interstitial myocarditis; focal myocardial necrosis; slight acute, focal interstitial pancreatitis; diffuse acute focal glomerulitis; focal hemorrhage of the right mamillary body; healed tuberculosis of the periportal and hilar lymph nodes, and focal and diffuse necrobiosis of the periportal lymph nodes.

CASE 2.—*Clinical History.*—G. C., a 15 year old white girl, entered the outpatient department of the Boston City Hospital in January 1939 with a complaint of stiffness and swelling of the hands of two weeks' duration. On examination macular erythematous lesions were observed on the fingers, and a diagnosis of lupus pernio was made. Several days later there appeared on the flush areas of the nose and cheeks an erythematous rash, which was considered to be characteristic of lupus erythematosus. At this time the urine contained albumin. Three Hinton tests of the blood gave doubtful reactions. Biopsy of a specimen from one of the lesions on the fingers showed hyperkeratosis and infiltration of the corium with lymphocytes and a few polymorphonuclear leukocytes. There was no evidence of sarcoid, tuberculosis or lupus pernio. Intramuscular injections of a bismuth compound were given, and for a time there appeared to be some improvement in the cutaneous lesions.

The patient was admitted to the hospital on May 9 with a complaint of abdominal pain, nausea and vomiting of three days' duration. The family history and the past history were noncontributory.

Physical Examination.—The patient was well developed and well nourished. Erythematous crusted lesions involved both cheeks and extended over the supraorbital ridges. Similar lesions were present on the arms, legs and fingers. Numerous ulcerations of the hard palate were observed. On examination the heart and lungs were normal. The blood pressure was 110 mm. of mercury systolic and 60 mm. diastolic. There was diffuse abdominal tenderness. The liver and the spleen were palpable, and there was a generalized enlargement of the lymph nodes.

Laboratory Data.—The urine contained albumin and occasional leukocytes and erythrocytes. The hemoglobin content of the blood on admission was 67 per cent (Sahli). A blood count showed 4,490,000 erythrocytes and 16,000 leukocytes per cubic millimeter. The blood thereafter contained between 4,600 and 8,000 leukocytes per cubic millimeter. The differential leukocyte count was normal. Three Hinton tests of the blood gave negative reactions. The total cholesterol content of the plasma was 82 mg. per hundred cubic centimeters, the nonprotein nitrogen concentration of the plasma 43 mg., the total plasma protein 6.84 Gm., with 2.9 Gm. of albumin and 3.9 Gm. of globulin, and the urea nitrogen content of the blood 18 mg.

Course of Illness.—The temperature on admission was 103 F. It fluctuated between 99 and 101 F. during the first week and thereafter remained normal. The pulse rate varied between 80 and 100 and the respiratory rate between 20 and 25. The abdominal pain and vomiting gradually subsided. The cutaneous lesions showed some regression, and the patient was discharged on June 1.

During the next eleven months the patient felt well and gained weight. Occasional lesions on the fingers developed in the winter months. She received weekly intramuscular injections of a bismuth compound. One month before her second admission to the hospital, following prolonged exposure to the sun, the facial lesions reappeared and persisted. Three days before admission malaise and fever developed. The patient was readmitted on June 3, 1940.

Physical Examination on Readmission.—The following abnormalities were now present: A confluent erythematous eruption involved the flush areas of the cheeks and the bridge of the nose. Multiple small ulcerations were present in the mouth and on the eyelids. On the volar surfaces of the hands were round, red, raised crusted lesions. There was a flame-shaped hemorrhage in the fundus of the right

eye. Basal and apical systolic cardiac murmurs were now audible. The blood pressure was 104 systolic and 60 diastolic. The liver and spleen were palpable, and there was a generalized enlargement of the lymph nodes.

Laboratory Data.—The urine contained large amounts of albumin, variable numbers of leukocytes and occasional granular casts. There was a 44 per cent excretion of phenolsulfonphthalein in the urine two hours after intravenous injection of the dye. The hemoglobin concentration was 75 per cent (Sahli). The blood count showed 3,850,000 erythrocytes and 5,250 leukocytes per cubic millimeter. The differential leukocyte count was normal. The per cent of hemoglobin and the erythrocyte count gradually fell. A few days before death the hemoglobin was 45 per cent (Sahli) and the total erythrocyte count 2,700,000 per cubic millimeter.

There was no growth of bacteria in four of six blood cultures. Streptococcus viridans was recovered from one blood culture and Staphylococcus albus from another. These were probably contaminants. Three Hinton tests of the blood gave positive reactions and two gave doubtful reactions. The Wassermann reaction of the blood was negative. The gonococcus complement fixation test of the serum gave a positive reaction once and a negative reaction once. The Widal reaction was negative. The sedimentation rate of the blood was elevated. The plasma prothrombin time was 50 per cent of normal. The coagulation time of the blood was thirteen minutes, and the bleeding time was three minutes.

On admission the nonprotein nitrogen content of the plasma was 41 mg. per hundred cubic centimeters. The sodium content of the serum was 130.6 milliequivalents per liter and the chloride content 104 milliequivalents per liter. The potassium content of the serum was 6.8 milliequivalents per liter. The calcium content of the serum was 8.5 mg., the phosphorus content 5.1 mg. and the phosphatase content 3.2 Bodansky units per hundred cubic centimeters. The total proteins of the plasma amounted to 6.6 Gm. per hundred cubic centimeters. The electrocardiogram showed a left ventricular preponderance. The T waves in leads I and II were flat, and that in lead IV was inverted.

Course of Illness.—The patient lived for five weeks following her second admission to the hospital. The temperature varied between 99 and 105 F. The pulse rate varied between 80 and 120 and the respiratory rate between 20 and 30. The major complaints were generalized abdominal pain, intractable vomiting and progressive asthenia. The lesions of the face and hands regressed while those in the mouth increased in severity.

Because of the low sodium and high potassium values observed in the serum on admission, large amounts of salt and carbohydrate were administered throughout the period of hospitalization. Subsequent determinations of serum sodium and potassium gave normal values. During the third week the patient became much worse. The fever and the pulse rate increased, and the blood pressure fell to 70 systolic and 50 diastolic. She vomited continually and complained of abdominal pain. On July 1, early in the fifth hospital week, 10 mg. of desoxycorticosterone acetate was administered subcutaneously, and this dosage was maintained until death. On this regimen there appeared to be improvement. The temperature fell from 105 to 99 F. and the pulse rate from 120 to 95. The blood pressure rose to 100 systolic and 50 diastolic. The vomiting and the abdominal pain were only partially relieved. On July 7, without any preceding apparent change in her condition, she suddenly died. Permission for autopsy was not obtained.

COMMENT

In each of the 2 cases presented, many of the characteristic clinical and laboratory findings of disseminated lupus erythematosus were encountered. Of particular interest were the additional manifestations suggestive of adrenal insufficiency. In each case, asthenia, nausea, vomiting, loss of weight and hypotension were prominent features. In the first case there was, in addition, a progressive pigmentation of the skin, which was first observed ten months prior to death and nine months before any erythematous lesions occurred. In the second case the potassium concentration in the serum was elevated prior to institution of therapy and subsequently returned to a normal value. In neither case was the chloride content of the serum lowered to a significant degree. Unfortunately, certain studies were not carried out which would have been of value in establishing or excluding a diagnosis of adrenal impairment. These tests include determinations of ketosteroids, studies of urinary chloride excretion and various types of dextrose tolerance tests.

There are few reported cases of disseminated lupus erythematosus with features suggesting adrenal insufficiency. Wendt[1] cited a case reported by Kraus and Bohac in which there were spotty pigmentation of the trunk and diffuse pigmentation of the sacral region. Addison's syndrome was not suspected clinically. At autopsy extensive necrosis of the adrenal glands and flecks of pigment in the mucous membranes of the upper part of the esophagus and lower part of the pharynx were present. In one of the cases reported by Wendt pigmentation of the entire body developed several weeks before death. There was no pigmentation of the mucous membrane, and the blood sugar and blood pressure were not reduced. At autopsy the adrenal glands were normal. In the case of dermatomyositis reported by Talbott, Gall, Consolazio and Coombs,[2] the clinical picture and the results of chemical examination of the blood were suggestive of Addison's disease. Several recent reports have stressed the possible relation of dermatomyositis and disseminated lupus erythematosus.[3] Brown pigmentation of the skin has

1. Wendt, H.: Interne Krankheitsbilder beim Lupus erythematodes acutus, München. med. Wchnschr. **81**:217-221 (Feb. 9) 1934.

2. Talbott, J. H.; Gall, E. A.; Consolazio, W. V., and Coombs, F. S.: Dermatomyositis with Scleroderma and Renal Endarteritis Associated with Focal Cortical Necrosis, Arch. Int. Med. **63**:476-496 (March) 1939.

3. (*a*) Keil, H.: Dermatomyositis and Systemic Lupus Erythematosus: I. Clinical Report of "Transitional" Cases with Consideration of Lead as Possible Etiologic Factor, Arch. Int. Med. **66**:109-139 (July) 1940; (*b*) Dermatomyositis and Systemic Lupus Erythematosus: II, ibid. **66**:339-383 (Aug.) 1940. (*c*) Banks, B. M.: Is There a Common Denominator in Scleroderma, Dermatomyositis, Disseminated Lupus Erythematosus, the Libman-Sacks Syndrome and Polyarteritis Nodosa? New England J. Med. **225**:433-444 (Sept. 18) 1941.

been observed in occasional cases of disseminated lupus erythematosus. Ludy and Corson [4] found a low serum chloride content in a patient with this disease.

The gross anatomic changes and the microscopic observations in cases of acute lupus erythematosus have been extremely variable. The

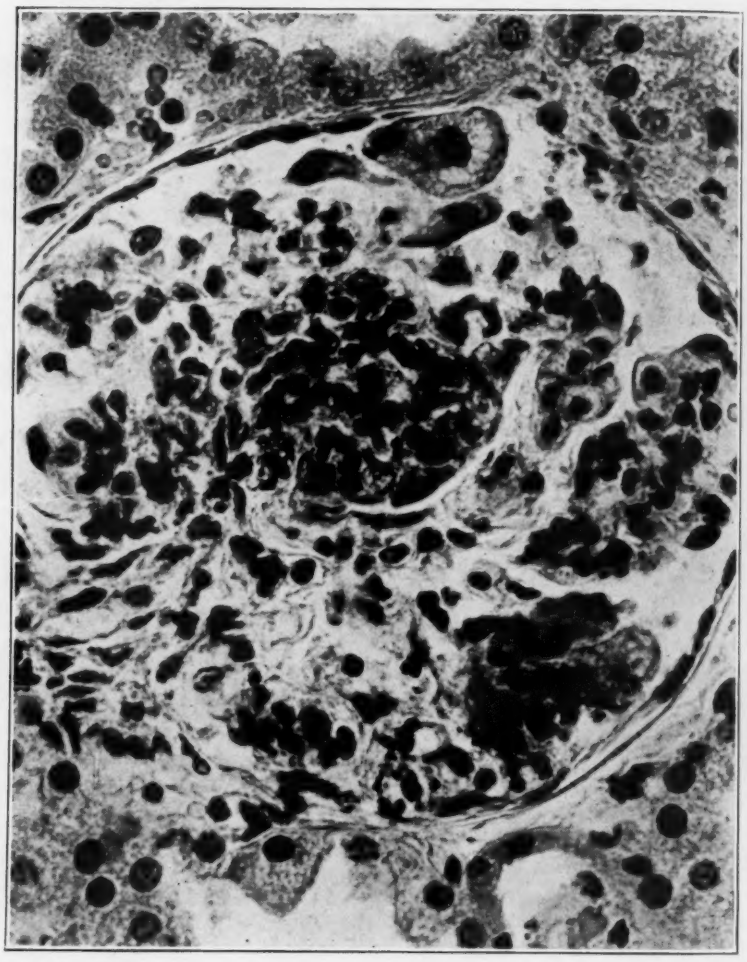

Fig. 1.—Glomerulus showing focal areas of necrosis and swollen vacuolated tuft epithelial cells.

autopsy in one of our cases presented certain interesting features. Involvement of the serous membrane was evidenced by extensive fibrous pleuritis and focal perisplenitis. Increased pericardial fluid, which was

4. Ludy, J. B., and Corson, E. F.: Lupus Erythematosus, Arch. Dermat. & Syph. **37**:403-416 (March) 1938.

present in our case, was observed in most of the cases mentioned by Mallory.[5] There was no evidence of endocarditis. Sections of myocardium showed focal changes which were similar to those described by Gross[6] in this condition.

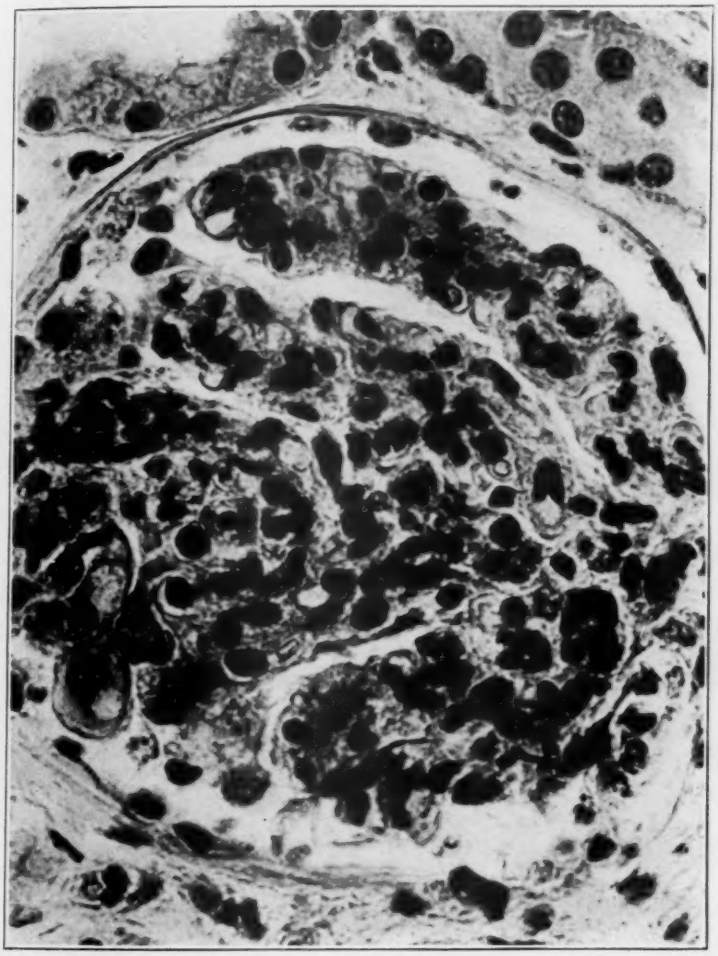

Fig. 2.—Glomerulus showing increased cellularity and swollen vacuolated tuft epithelial cells.

The most interesting changes were those observed in the kidneys in our case. The focal irregular thickening of the glomerular basement

5. Mallory, T. B., in discussion on Acute Disseminated Lupus Erythematosus, Cabot Case 24341, New England J. Med. **219**:273-277 (Aug. 25) 1938.

6. Gross, L.: The Cardiac Lesions in Libman-Sacks Disease with a Consideration of Its Relationship to Acute Diffuse Lupus Erythematosus, Am. J. Path. **16**:375-407 (July) 1940.

membrane which constitutes the "wire loop lesion" of Baehr, Klemperer and Schifrin [7] was present. In addition, the glomeruli were swollen and ischemic and showed an increased cellularity due largely to a proliferation of tuft endothelial cells. Focal glomerular changes included areas of necrosis, swollen tuft epithelial cells and intracapillary fibers.

Fig. 3.—Glomerulus showing diffuse irregular thickening and hyalinization of the basement membrane and focal intracapillary hyaline fibers (Lee-Brown connective tissue and basement membrane stain).

7. Baehr, G.; Klemperer, P., and Schifrin, A.: A Diffuse Disease of the Peripheral Circulation, Usually Associated with Lupus Erythematosus and Endocarditis, Tr. A. Am. Physicians **50**:139-155, 1935.

Somewhat similar focal changes in the glomeruli have been observed by others.[8] Although the majority of kidneys which have been observed in cases of this disease do not show these focal changes, it is our belief that similar focal changes have not been observed in any other disease.

Fig. 4.—Glomerulus showing, to greater degree than in figure 3, diffuse irregular thickening and hyalinization of the basement membrane (Lee-Brown stain).

8. (*a*) Ginzler, A. M., and Fox, T.: Disseminated Lupus Erythematosus, Arch. Int. Med. **65**:26-50 (Jan.) 1940. (*b*) Baehr, Klemperer and Schifrin.[7] (*c*) Denzer, B. S., and Blumenthal, S.: Acute Lupus Erythematosus Disseminatus, Am. J. Dis. Child. **53**:525-540 (Feb.) 1937. (*d*) Weiner, A. L.: Disseminated Lupus Erythematosus Treated by Sulfanilamide, Arch. Dermat. & Syph. **41**:534-544 (March) 1940.

It was disappointing that no significant abnormality could be demonstrated in the adrenal glands. Guttman [9] made a statistical analysis of 566 cases of Addison's disease in which autopsy was performed, and in all but 4 definite pathologic changes were present in the adrenal glands. In the 4 cases in which the adrenal glands were normal the clinical evidence favoring the diagnosis of Addison's disease was unconvincing. The findings of Wendt [1] as regards the adrenal glands in lupus erythematosus have been mentioned previously.

Widespread vascular lesions have been observed frequently in this disease.[10] In our autopsy vascular lesions were confined to the glomeruli and to the right mamillary body, where there were focal hemorrhages.

The periportal lymph nodes presented focal areas of necrosis or necrobiosis similar to that described in a case reported by Ginzler and Fox.[8a] In addition, evidence of healed tuberculosis in the periportal and hilar lymph nodes was presented in our case. There was no microscopic evidence of any active tuberculous lesion. The association of inactive tuberculosis and necrobiosis was observed by Keil [3b] in the hilar lymph nodes in acute lupus erythematosus.

SUMMARY

Two cases of acute lupus erythematosus are reported, in each of which there were certain clinical and laboratory findings suggestive of adrenal insufficiency. In neither was the complete syndrome of Addison's disease present. However, the similarity to this condition was more striking than is commonly observed in a chronic wasting disease. The autopsy observations in 1 case are discussed. No significant abnormality was present in the adrenal glands. Unusual pathologic lesions were observed in the kidneys and lymph nodes.

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9. Guttman, P. H.: Addison's Disease, Arch. Path. **10**:742-785 (Nov.); 895-935 (Dec.) 1930.

10. Acute Disseminated Lupus Erythematosus, Cabot Case 24201, New England J. Med. **218**:838-843 (May 19) 1938. Reifenstein, E. C.; Reifenstein, E. C., Jr., and Reifenstein, G. H.: A Variable Symptom Complex of Undetermined Etiology with Fatal Termination, Arch. Int. Med. **63**:553-574 (March) 1939. Ludy and Corson.[4] Baehr, Klemperer and Schifrin.[7]

SYMMETRIC SYPHILITIC GRANULOMAS OF THE ELBOWS

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Symmetric granulomatous nodules appearing about the elbows and clinically resembling benign tumors present a rare manifestation of the late stage of syphilis. Howard Fox [1] described the case of a Negress who had hard symmetric subcutaneous nodules on the elbows and knees. He mentioned a similar case reported by Goodman and Young [2] in which the patient had symmetric masses on the elbows and a nodule on one knee. Milch and Galland [3] reported 5 instances of tumor-like masses occurring "in or about muscles" in which the syphilitic nature was not recognized until after surgical removal. The juxta-articular nodules which have been discussed by Manson-Bahr [4] and Stitt [5] and are found particularly among the natives in certain tropical countries are similar and are a late manifestation of either syphilis or yaws.

REPORT OF A CASE

A white man aged 49, a chauffeur, entered Grant Hospital complaining of hard swellings on both elbows. The nodules had been present for more than fifteen years and had greatly increased in size. Recently he had noticed slight pain; otherwise the nodules had caused him no trouble. The red blood cell count on admission was 3,800,000 per cubic millimeter, and the white blood cell count was 9,600. The hemoglobin concentration of the blood was 11.5 Gm. per hundred cubic centimeters. Serologic tests were not made until after the microscopic studies had been completed, and then the Wassermann and Kahn reactions of the blood were found

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1. Fox, H.: Subcutaneous Fibroid Syphilomas of Elbows and Knees, a Rare Manifestation of Syphilis, Arch. Dermat. & Syph. **5**:198 (Feb.) 1922.

2. Goodman, H., and Young, W. J.: Clinical Pathological Study of an Unusual Syphilitic Manifestation Resembling Juxta-Articular Nodules, Am. J. M. Sc. **159**:231, 1920.

3. Milch, H., and Galland, W.: Pseudoneoplastic Luetic Granulomata, Am. J. M. Sc. **182**:405, 1931.

4. Manson-Bahr, P. H.: Manson's Tropical Diseases, ed. 11, Baltimore, Williams & Wilkins Company, 1940, p. 633.

5. Stitt, E. R.: Diagnostics and Treatment of Tropical Diseases, ed. 5, Philadelphia, P. Blakiston's Son & Co., 1929, p. 166.

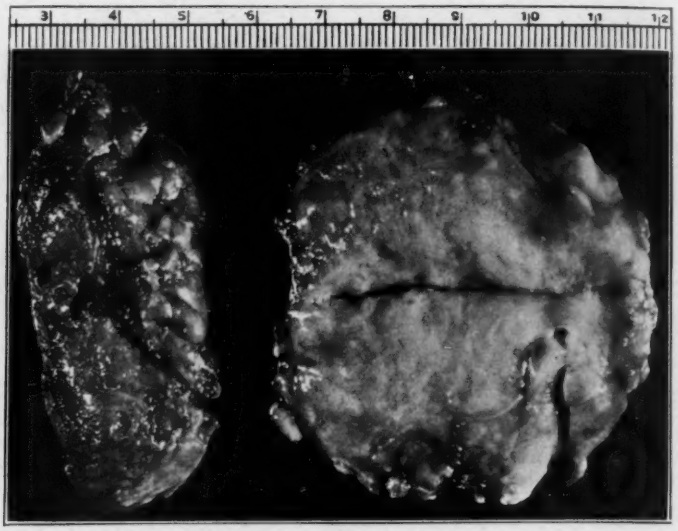

Fig. 1.—Granulomatous nodules removed from the region of the elbows. The lobulated character of one nodule is shown to the left and the cut surface of the other to the right.

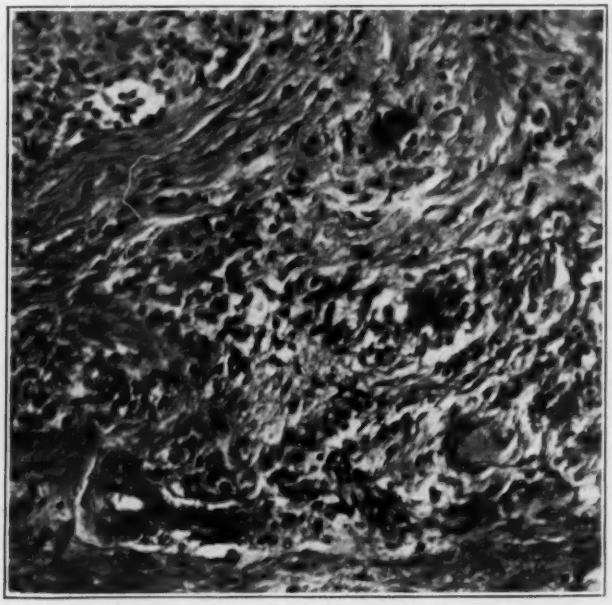

Fig. 2.—Dense strands of connective tissue and cellular areas with giant cells of the Langhans type (× 112).

to be strongly positive. Roentgen ray examination showed the chest to be normal. No tertiary lesions of the skin were noted, and there were no nodules on the anterior surfaces of the tibias.

The tumor-like masses were excised by Dr. Sylvan Coombs and Dr. Robert Coombs. The masses were unattached to the skin and slightly movable and covered the sharp ridge or posterior border of the ulna, beginning at the apex of the posterior surface of the olecranon and extending along the ulnar border.

The surgical specimens consisted of two hard oval masses, one measuring 6.5 by 3 by 2 cm. and the other 5.5 by 3 by 2 cm. The surfaces presented numerous nodular elevations. The surfaces made by sectioning were pale gray and traversed by irregular wide bands of fibrous tissue.

Microscopic examination showed large amounts of dense fibrous tissue between which were granulomatous accumulations of epithelioid cells with lymphocytes and plasma cells and an occasional Langhans type of giant cell. Around some of the small thickened blood vessels toward the periphery there were dense accumulations of plasma cells. No necrotic areas were seen in the sections. The sudan III stain showed no fat droplets. Levaditi stains for spirochetes revealed none.

When the bilateral masses were removed, a gross diagnosis of xanthofibroma of tendon sheath origin was seriously considered. There were no cutaneous lesions which might have suggested syphilis. A traumatic factor was investigated, but the patient's occupation as a chauffeur did not suggest any relation. Frozen sections revealed the granulomatous nature of the nodules. The softest portions of the fresh material were ground up and injected into guinea pigs. A study of the paraffin sections showed numerous plasma cells in the cellular areas, which suggested syphilis rather than tuberculosis. The Wassermann and Kahn reactions were later found to be strongly positive.

COMMENT

Weber [6] used the term syphiloma and not gumma for nodules when necrotic and gummous areas were absent and fibrotic and cellular areas predominated. Schamberg [7] suggested that this type of dense fibrotic reaction might be expected to be seen more frequently in the Negro race.

In the differential diagnosis true tumors, such as fibroma, xanthoma, lipoma, desmoids and fibrosarcoma, arising from the fasciae and tendon sheaths should be considered. Tuberculosis presents the most common granulomatous lesion, from which a late syphilitic process must be differentiated. Mason,[8] in connection with the differential diagnosis of tuberculous tenosynovitis of the hand, stated that syphilitic tenosynovitis, which is rare, is more likely to be bilateral than the tuberculous type. Subcutaneous sporotrichotic nodules of the forearms as described

6. Weber, F. P.: Chronic Fibroid Subcutaneous Syphilomata of the Legs, Associated with Chronic Peri-Urethral Induration in the Penis (So-Called "Induratio Penis Plastica"), Brit. J. Dermat. **32**:173, 1920.

7. Schamberg, J. L., in discussion on Fox.[1]

8. Mason, M. L.: Tuberculous Tenosynovitis of the Hand, Surg., Gynec. & Obst. **59**:363, 1934.

by Curtis [9] would present no difficulty in differential diagnosis, since these nodules are usually disseminated, ulcerate early and are of much shorter duration.

The soft tissues which may be involved in a syphilitic sclerogummatous process in addition to muscles are structures such as the fasciae, aponeuroses, tendons, tendon sheaths and bursae. In many cases the exact origin cannot be designated. Goodman and Young [2] interpreted the nodules described in their patient as being derived from the tendons. Fox [1] was not certain whether the lesions on the knees of his patient were connected with the ligamentum patellae, but the nodules on the elbows definitely had no tendinous origin. Instances in which the bursae have been definitely involved have been reviewed by Churchman.[10] In the case reported in this paper there was an intimate relation to the aponeuroses attached to the ulnar border.

SUMMARY

A case of syphilis in the late stages is reported in which the rare manifestation of bilateral symmetric syphilitic granuloma on the elbows is presented. The necessity for a serologic study before operations involving masses "in or about" muscles is stressed.

9. Curtis, G. H.: Disseminated, Subcutaneous, Gummatous, Ulcerative Sporotrichosis (S. Schenckii-Beurmannii), Cleveland Clin. Quart. **5**:57, 1938.

10. Churchman, J. W.: Luetic Bursotherapy of Verneuil, Am. J. M. Sc. **138**: 371, 1909.

USE OF SULFANILAMIDE AND ITS DERIVATIVES IN OINTMENT FORM

LOCAL TREATMENT OF CUTANEOUS DISEASES

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Sulfanilamide and its derivatives are now being applied in a constantly increasing variety of forms in the treatment of a steadily widening group of dermatoses. In recent months a number of investigators have reported remarkably favorable results from the use of such drugs incorporated in ointment bases. Brunsting [1] used a 4 per cent sulfanilamide ointment for impetigo contagiosa. Lain [2] had success with sulfanilamide in glycerin in the local treatment of various pyodermas. Schnieper,[3] reporting on 124 patients treated with a 5 per cent sulfathiazole ointment, recommended its use for superficial pyogenic infections. Sams and Capland [4] successfully treated 53 patients (35 with impetigo contagiosa and 12 with ecthyma) with a 5 to 25 per cent sulfathiazole ointment or with sulfathiazole powder. Keeney, Pembroke, Chatard and Ziegler [5] reported curing 8 patients with secondary infection of infantile eczema in seventy-two hours and 10 patients with impetigo contagiosa in seven days with sulfathiazole ointment.

METHOD OF STUDY

A total of 115 patients have been treated during the past year with sulfanilamide and its derivatives in ointment bases. The majority of these patients were treated in the outpatient clinic.

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The ointments used in this investigation were supplied by the Abbott Laboratories, North Chicago, Ill., and the Winthrop Chemical Co., Inc., New York.

1. Brunsting, L. A.: Treatment of Common Diseases of the Skin, Journal-Lancet **60**:438 (Oct.) 1940.

2. Lain, E. S.: Sulfanilamide in Glycerin in Local Treatment for Pyodermas, Arch. Dermat. & Syph. **44**:257-258 (Aug.) 1941.

3. Schnieper, A.: La chimiothérapie locale par les dérivés sulfamidés et par l'onguent cibazol en particulier, Schweiz. med. Wchnschr. **71**:222-225 (March 8) 1941.

4. Sams, W. M., and Capland, L.: Topical Treatment with Sulfathiazole, Arch. Dermat. & Syph. **44**:226-230 (Aug.) 1941.

5. Keeney, E. L.; Pembroke, R. H.; Chatard, F. E., and Ziegler, J. M.: Sulfathiazole Ointment in the Treatment of Cutaneous Infections, J. A. M. A. **117**:1415-1417 (Oct. 25) 1941.

The preparations used were sulfanilamide, sulfathiazole (2-[para-aminobenzenesulfonamido]-thiazole), sodium sulfathiazole and sulfadiazine (2-[paraaminobenzenesulfonamido]-pyrimidine) in strengths varying from 5 to 50 per cent. They were incorporated in two different bases, which were essentially water in oil emulsions. The base most frequently used contained diethanolamine oleate, white wax, liquid petrolatum, white petrolatum and distilled water. The preparation was compounded so that the drugs were in a suspended state, the size of the suspension approaching a colloidal one. They were in solution to about the degree of their solubility in water (0.8 per cent in the case of sulfanilamide and 0.1 per cent in the case of sulfathiazole).

The dermatoses treated may be grouped as follows: (1) primary infections of the skin, (2) diseases of the skin with secondary pyogenic infections and (3) miscellaneous diseases.

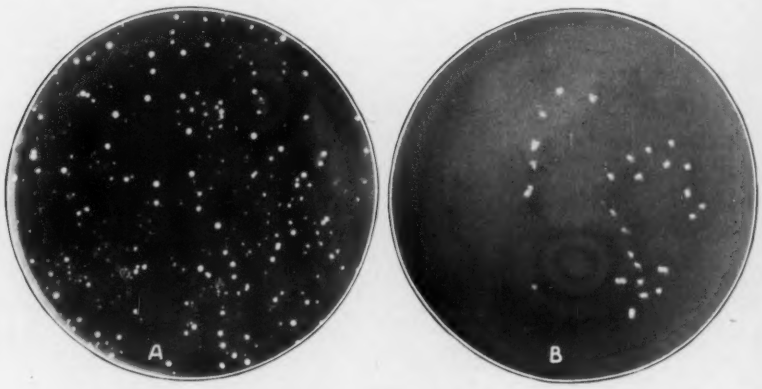

Fig. 1.—Cultures on blood agar of material from lesions of patient with ecthyma, the one at the left made before treatment and the one at the right after sulfathiazole ointment had been used for one week.

An attempt was made to control the experiment by a laboratory check. Cultures were made of material obtained with a wire loop from a moist lesion or from under a crust after the skin had been cleaned with alcohol. The loop was inserted into tubes containing 10 cc. of melted agar, which had been cooled to 42 C. in a water bath and to which had been added 1 cc. of fresh citrated human blood. Of this mixture 0.5 cc. was then pipetted from the tube into a similar second tube of blood agar. Plates were poured from these tubes, which were incubated at 37 C., and the total number of colonies in each plate was counted after thirty-six to forty-eight hours. The same procedure was followed at subsequent visits. Some 37 cases were followed in this manner. Often the number of colonies in the first plate could not be counted, and occasionally counts as high as 760 were found in the diluted

second plate. A close correlation was noted between the number of colonies and the clinical condition. Relapses were evidenced by rising counts, and completely negative plates were common after a week's treatment with the ointment.

RESULTS OF TREATMENT

A. Primary Infections of the Skin.—1. Impetigo Contagiosa (Forty-five Patients): All except 1 patient were cured in three to ten days, an average of six days. Fourteen patients had used ammoniated mercury and 7 had used gentian violet previously without benefit. Hot compresses of boric acid were used twice a day, followed by the application of the ointment twice a day. The majority of the patients were treated with sulfanilamide or sulfathiazole ointment with equally good results. More recently a few received sulfadiazine ointment, with less dramatic results.

2. Ecthyma (Twelve Patients): All were cured in ten to twenty-five days.

3. Sycosis Vulgaris (Twelve Patients): Three were cured in from one to three months. One of these had a recurrence, which cleared up in two weeks. Two patients were cured by the use of fractional doses of roentgen rays (75 r) in conjunction with the ointment. These 5 patients have been observed for two to six months and have remained well. Three patients were improved for several months by using the ointment, but new lesions continue to develop. Encouraging results were obtained in 3 of these refractory patients by Dr. F. P. Lowenfish with sodium sulfathiazole introduced by cataphoresis. Sulfathiazole by mouth in 3 patients produced no beneficial effect. One patient became sensitized to sulfathiazole while using the ointment.

4. Folliculitis of the Scalp (Two Patients): One patient responded favorably after six weeks. The other patient, although improved, was not completely cured even after three months.

5. Acne Varioliformis (Three Patients): All patients responded to treatment within a week to ten days. One showed a recurrence two months later but responded favorably to reapplications of the ointment.

6. Dermatitis Repens (One Patient): The patient was greatly improved after two weeks of treatment and remained so for two months but then had a relapse and was much worse than he had been before.

B. Secondary Bacterial Infections Occurring in Other Diseases.—1. Infantile Eczema (Five Patients): The secondary infections cleared in fourteen days in 4 patients and in thirty days in 1 patient. The essential condition remained unchanged in all of them.

2. Chronic Dermatitis of the Fingers of Unknown Origin (Three Patients): The conditions in these patients were recalcitrant to many

types of treatment used previously. In 1 patient the dermatitis cleared in one month, relapsed three months later and was in the end uninfluenced by this treatment. Two patients showed an up and down course under the treatment and were finally dismissed with their conditions unimproved.

3. Allergic Eczema with Secondary Infection (Three Patients): All were cleared of their secondary infection in ten to twenty-four days, but the essential condition remained unchanged.

4. Dermatophytosis with Secondary Infection (Five Patients): All were relieved of the secondary infection in three to ten days, but the primary condition did not yield to this form of treatment.

5. Epidermolysis Bullosa (Five Patients): Two patients in whom chronic secondary infection played the major role in the persistence of the lesions were greatly improved. The 3 remaining patients were uninfluenced by this treatment.

6. Psoriasis (Two Patients): In both patients the secondary infection cleared but the psoriasis was not affected.

7. Acne Vulgaris of the Pustular Type (Six Patients): Only slight improvement was noted.

8. Seborrheic Dermatitis (Six Patients): There was little permanent benefit.

9. Pustular Bacterid (Five Patients): There was no permanent benefit.

REACTIONS

Severe reactions were noted in 2 patients receiving sulfathiazole ointment. The first patient was a Negress aged 17, who had impetigo on the right cheek of two weeks' duration. She was treated with 50 per cent sulfathiazole ointment for ten days, at the end of which time a definite dermatitis with pinhead-sized vesicles was noted around the lesion, with a few similar pinhead-sized vesicles on the opposite cheek and edema of the upper eyelids. A weaker (25 per cent) sulfathiazole ointment was substituted, and treatment was continued for two days, by which time the lesion had become raw and oozing. The use of sulfathiazole ointment was discontinued, and treatment with 2 per cent gentian violet was begun. The patient was observed five days later, at which time follicular vesicopustules, grouped in dime-sized to palm-sized lesions, were present on both thighs and forearms. The temperature and blood count were normal. Culture of material from the lesion and inoculation of a rabbit's cornea were negative for herpes simplex virus. Two days later other lesions similar to those described were noted on the abdomen and back. Improvement began two days later, and the patient was well in three weeks. A patch test with the ointment base

gave negative results. Treatment consisted of gentian violet during the acute stage of the dermatitis followed by paste of zinc oxide N. F.

The second patient was a Negro aged 45 with sycosis vulgaris on the face of many years' duration. He was treated for one week with 50 per cent sulfathiazole ointment. At the end of that time the sycosis was improved but itching was present. When 25 per cent sulfathiazole ointment was substituted, the patient showed improvement for one week,

Fig. 2.—The left thigh of the patient with a generalized dermatitis resulting from local application of 50 per cent sulfathiazole ointment on the face.

but then the same clinical picture developed as that described in the previous case. Treatment and recovery were likewise the same. Two months later the patient was given two tablets of sulfathiazole, 0.5 Gm. each, by mouth. Within two hours the eyelids were swollen shut, and an identical eruption appeared in the same locations (face, forearms, back, abdomen and thighs) as before. The patient was not seen for two days after this reaction. At this time the sulfathiazole level of the blood was zero.

Two patients showed mild reactions to 10 per cent sulfathiazole ointment, which consisted of pinhead-sized vesicles around the lesions. The reaction subsided when sulfanilamide ointment was used but recurred on repeated application of sulfathiazole ointment.

One patient with varicose eczema had a generalized scarlatiniform eruption while using sulfathiazole ointment. She was receiving simultaneously injections of sodium salicylate for varicose veins. The eruption cleared while the ointment base was being used but recurred mildly when sulfathiazole ointment was again used.

COMMENT

In this study 115 patients with various dermatoses were treated with sulfanilamide, sulfathiazole, sodium sulfathiazole and sulfadiazine in concentrations of 5 to 50 per cent in ointment bases. Cure was obtained in all patients with superficial pyogenic infections, whether primary—such as impetigo and ecthyma—or secondary—such as those occurring in allergic eczema, psoriasis and dermatophytosis.

In deeper-seated infections, however, these ointments were less effective, probably because of their limited ability to reach the seat of the infection. This fact would explain the varying results obtained in the 12 patients with sycosis. Three of these were apparently cured, but the other 9 did not have decisive results.

The time required to effect a cure in the 45 cases of impetigo was six days on an average, as compared with five to twenty-five days reported by Sulzberger and Wolf [6] and fifteen days recorded by Pratt, Imhoff and Decker [7] with other remedies.

The results in pustular acne and seborrheic dermatitis were inferior to those obtained with accepted methods of treatment. Allergic eczema, psoriasis and pustular bacterid were not favorably affected by this treatment.

The only reactions noted occurred in the patients treated with sulfathiazole ointment. This observation parallels results obtained when sulfanilamide and its derivatives were given by mouth; sulfathiazole showed a greater tendency to produce eruptions. The 2 severe reactions to sulfathiazole occurred in the earlier cases, when a higher concentration (50 per cent) was being used. Sams and Capland [4] reported a somewhat similar experience when they used sulfathiazole powder locally. There is little doubt that the reactions were due to the sulfathiazole, as patch tests with the ointment base elicited no reactions and administration of sulfathiazole by mouth to 1 patient reproduced the eruption.

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6. Sulzberger, M. B., and Wolf, J.: Dermatologic Therapy, Chicago, The Year Book Publishers, Inc., 1940.

7. Pratt, A. G.; Imhoff, R. E., and Decker, H. B.: Impetigo Contagiosa Treated with Ammoniated Mercury-Colloidal Kaolin Lotion, J. M. Soc. New Jersey **36**:442 (July) 1939.

Since the concentration of the sulfathiazole has been reduced to 5 per cent no severe reaction has occurred. These results suggest the necessity for caution in the application of high concentrations of these drugs to the skin. There is also danger of sensitizing the patient by local application of the drugs, thus precluding their future use by mouth for other diseases. This is illustrated by the patient sensitized by sulfathiazole ointment who had a severe cutaneous reaction when subsequently given sulfathiazole by mouth.

Sulfanilamide seemed to be as effective as sulfathiazole ointment even in patients infected with Staphylococcus aureus. This result is in contrast with the greater efficacy of sulfathiazole over sulfanilamide when administered internally in cases of staphylococcic infections. Perhaps the explanation for the equal effects of the two drugs used locally lies in the greater solubility of sulfanilamide in water.

Sulfadiazine was used in a few cases toward the end of the study, but the results were not as dramatic as those obtained with sulfanilamide and sulfathiazole ointments.

Sodium sulfathiazole also showed no greater efficacy than the others, and because of greater alkalinity it is more likely to produce irritation.

A 5 per cent concentration of each drug was found just as effective as higher concentrations and less productive of reactions. The ointments were white and odorless and were not objectionable to the users. In most cases no dressings were required.

SUMMARY AND CONCLUSIONS

A series of 115 patients with various dermatoses treated with 5 to 50 per cent sulfanilamide, sulfathiazole, sulfadiazine and sodium sulfathiazole ointments is reported.

Cure was obtained in all patients with superficial pyogenic infections, such as impetigo, in a shorter average time than that reported with accepted methods of treatment. In patients with cutaneous diseases secondarily infected, the secondary infections were quickly cured, but further treatment with the ointment did not favorably affect the primary disease.

Results in patients with deeper pyogenic infection, such as sycosis, were variable, apparently depending on the ability of the ointment to reach the seat of the infection.

Sulfathiazole ointment produced the only reactions noted. This ointment in 50 per cent concentration produced an unusual and apparently characteristic reaction in 2 patients. The identical reaction was subsequently produced in one of these patients by giving sulfathiazole by mouth.

A 5 per cent concentration of sulfanilamide or sulfathiazole ointment is recommended.

TOXIC ERUPTIONS DUE TO PHENOBARBITAL

REPORT OF TWO CASES

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AND
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Phenobarbital, introduced to the medical profession as recently as 1911, has proved a useful sedative and hypnotic drug. However, Loewe [1] soon recognized that toxic manifestations might arise from its use. In spite of its increasingly widespread use, Menninger,[2] in 1928, could find only 41 reported cases of cutaneous eruptions. Undoubtedly, many others had gone unrecognized. Since 1928 the number of reports has increased and fatalities have been encountered, so that by 1934 a total of 408 deaths due to barbiturates had been recorded in the literature.[3] Various eruptions have been described as due to the use of phenobarbital. However, it is not generally recognized that from 1 to 5 per cent of persons taking the drug will show a toxic rash [4] and that these reactions may be so severe as to cause death.[5]

It is our desire to emphasize again the dangers inherent in the use of phenobarbital and to report 2 cases in which toxic reactions to the drug were manifested in the form of a severe exudative and exfoliative dermatitis, from which there was eventual recovery.

REPORT OF CASES

CASE 1.—A. M., a 46 year old white woman, was admitted to the hospital on April 16, 1941 because of an extensive eruption, involving the skin, mucous membranes and conjunctivas, of seven days' duration.

Because of symptoms of the menopause, phenobarbital, 30 mg. three times daily, had been prescribed on March 20, 1941 at another hospital. Three dozen

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1. Loewe, S.: Klinische Erfahrungen mit Luminal, Deutsche med. Wchnschr. **42**:947, 1912; cited by Wile and Benson.[5a]

2. Menninger, W. C.: Skin Eruptions with Phenobarbital, J. A. M. A. **91**:14 (July 7) 1928.

3. Scarlett, E. P., and MacNab, D. S.: Poisoning from Phenobarbital with Report of a Fatal Case and Review of Fatalities Previously Reported, Canad. M. A. J. **33**:635 (Dec.) 1935.

4. Menninger.[2] Scarlett and MacNab.[3]

5. (*a*) Wile, U. J., and Benson, J. A.: Exfoliative Dermatitis Due to Phenobarbital with Fatal Outcome: Report of Two Cases, Ann. Int. Med. **13**:1243 (Jan.) 1940. (*b*) Scarlett and MacNab.[3]

pills (1.08 Gm.) were given, with renewal of the medication on April 4, when she returned for a check-up. She continued taking the same dose for the next five days, so that her total intake of phenobarbital was 1.53 Gm. On April 9, because of a sore mouth, a fever and a cutaneous eruption, she called a physician, who advised stopping the taking of the pills, forcing fluids and gargling with sodium perborate solution.

On April 11 she was first seen by one of us. By then the eruption was generalized, consisting of discrete bright red macular and papular lesions, more pronounced on the extensor surfaces, but with a moderate distribution on the flexor surfaces, the palms and the soles. This was accompanied by some burning. The mucous membranes of the mouth showed extensive erosions, covered by a dirty grayish, membranous exudate, and there were profuse salivation and drooling. The vaginal mucosa likewise showed extensive ulcerations, covered by a similar exudate, and there was a profuse discharge. Conjunctival and scleral injection was marked, and photophobia was present. During the ensuing week all symptoms progressed. Large, confluent lesions became prominent on the body. Hemorrhagic

Fig. 1 (case 1).—Crusted lesions on the face and extensive eruption on the arms and back due to phenobarbital.

vesicles and bullae appeared on the plantar surfaces of the toes; the skin between these extensive lesions assumed a violaceous hue. Vesicles developed in the mouth, about the lips and on the cheeks. These ruptured shortly after their appearance, giving rise to a bloody discharge from the mouth and black hemorrhagic crusts on the lips and face. A similar reaction occurred on the vulva. Burning on urination was noted. The eyelids were swollen and were stuck together by a thick, purulent exudate that covered the conjunctivas and corneas, obscuring vision. She finally consented to enter the hospital on April 16.

On admission physical examination showed chiefly the condition of the cutaneous and mucosal surfaces. There was a generalized papulovesicular eruption. Many of the lesions had become confluent and were covered with tough hemorrhagic crusts, which were prominent on the cheeks, nares, back and extensor surfaces of the arms (fig. 1). The conjunctivas were intensely red and were covered with a thick exudate. Deep fissures marked the swollen lips. Large areas of the buccal mucosa appeared raw and in places necrotic. Hemorrhagic spots covered the hard and soft palates. The pharyngeal mucosa was injected, and the tongue was

swollen and painful. A profuse viscid bloody discharge exuded from the mouth. The vulva and vagina presented a similar appearance and discharge. There were large, tender, external hemorrhoids, which bled readily.

During the first ten days the urine contained a trace of albumin and many white and red cells in the sediment. Thereafter the urine rapidly became and remained normal. The Wassermann, Kahn and Hinton reactions of the blood were negative. There was never any anemia, and the platelet count was normal. White blood cells on admission numbered 5,300, with 63 per cent polymorphonuclear leukocytes, 23 per cent lymphocytes, 8 per cent monocytes and 6 per cent eosinophils. Thereafter the white cells ranged between 6,000 and 10,000, and the eosinophils disappeared from the smears after the third day. There was no nitrogen retention in the blood and no jaundice. The stools never showed more than a 2 plus guaiac reaction for occult blood and generally gave a negative reaction. Cultures of material from the conjunctivas grew Staphylococcus aureus and a hemolytic streptococcus. The mouth showed Staphylococcus albus, fusiform bacilli and spirilla. No gonococci were found by smear or by culture in the vaginal discharge. Culture of the urine revealed nonhemolytic Staph. aureus.

The rectal temperature hovered between 101 and 102 F. during the first three days. After the fifth day it never exceeded 100 F. Because of the extensive rash fluids were not given parenterally, but by careful supervision it was possible to get the patient to swallow about 2 to 2½ liters of fluid daily, despite her fear of being choked by the viscid oral exudate. The output of urine was never depressed. A daily sponge bath was given, followed by gentle applications of boric acid ointment to the skin. The conjunctival sacs were irrigated every hour, and hot packs were applied to the eyes constantly between irrigations. A dilute solution of hydrogen peroxide was used as a mouth wash, supplemented after the third week by topical application of 2 per cent aqueous solution of gentian violet to the denuded areas. Frequent vulvar irrigations with warm boric acid solution were given throughout her stay. After the third day, nicotinic acid, a preparation of fish liver oils (navitol), riboflavin and brewers' yeast supplemented her meager liquid diet.

Improvement on this regimen was rapid. After ten days both the skin and the mucous membranes showed decided improvement. Desquamation began and resulted in the loss of large sheets of skin from many parts, especially from the palms and soles. Areas of brownish pigmentation remained to mark many of the parts affected. All the nails were slowly shed. By August, three months after the patient's discharge from the hospital, regrowth of the nails was complete, the pigmentation of the skin was fading and all the mucous membranes appeared normal.

Case 2.—U. B., a 50 year old Negress, was admitted to the hospital on Oct. 12, 1941 because of burning and swelling of the eyes, swelling of the mouth and sore throat of six hours' duration.

The patient first came to the outpatient department of this hospital in July 1941, complaining of a painful lump in her right groin that had developed over a period of several weeks. A deep reddish, nonitching, maculopapular eruption was scattered symmetrically over the extremities and the body. A depressed scar, 1 cm. in diameter, was present just inside the vaginal introitus on the right side. Serologic reactions for syphilis were positive. A diagnosis of secondary syphilis was made, and treatment was begun with clorarsen (phenarsine hydrochloride, a trivalent arsenical recently introduced for the treatment of syphilis), intravenously, the weekly dose being 45 mg. The inguinal node regressed strikingly, and the

rash disappeared rapidly. Except for some nausea following the first injection, no untoward reaction to the drug was noted. She received ten injections before admission.

Because of insomnia and nervousness she was advised, forty days before admission, to take 30 mg. of phenobarbital four times daily. She continued taking this medication until the day of admission, taking a total of 4.8 Gm. On October 10, two days before admission, she received her last injection of clorarsen. The next morning she found her eyelids stuck together. Throughout the day her eyes smarted, felt full of sand and were red. Irrigation of the eyes with boric acid solution gave no relief. The next morning her eyelids were puffy and glued together, her lips were swollen and her mouth and throat were sore. She entered the hospital in the afternoon.

Physical examination confirmed the presence of severe scleral and conjunctival injection, with edema of the lids, lacrimation and photophobia. Her vision, pupillary reflexes, extraocular muscles and ocular fundi were unaffected. The nasal mucosa was red and edematous. The lips were edematous, and the gingival surfaces showed several gray patches, 2 to 3 mm. across, that could be scraped off, revealing a raw base. Similar patches were scattered over the buccal surfaces, the hard palate and the pharynx. The tongue was heavily coated. The voice was hoarse and indistinct. Two small reddish maculopapular lesions were present over the sternum, and the skin of the arms and hands had a violaceous hue. Otherwise the skin and its appendages were not abnormal. Moderately enlarged, nontender inguinal nodes were present bilaterally without other adenopathy. Vaginal examination revealed only the scar mentioned. Her blood pressure and reflexes were normal. Examination of the lungs, heart and abdomen was noncontributory.

On admission, the urine showed a specific gravity of 1.021, with no albumin or sugar but with 8 to 10 white blood cells and occasional red blood cells per high power field of the sediment. After the third day the urine always contained albumin, although the amount declined to a slightest perceptible trace before discharge. For two weeks the sediment showed many white blood cells, with occasional red blood cells. The hemoglobin content of the blood was 79 per cent on admission; the red cell count was 4,150,000 and the white cell count 11,350, with 77 per cent polymorphonuclear leukocytes, 18 per cent lymphocytes, 4 per cent monocytes and 1 per cent eosinophils. A slight anemia developed during her stay, but the leukocyte count never rose any higher and was generally normal. Eosinophils rose to 5 per cent only once. There was no nitrogen retention and no jaundice. The stools were examined for arsenic, without success. Guaiac reactions for occult blood in the stools were consistently negative. Cultures of the throat and mouth revealed a normal flora and no Klebs-Löffler bacilli. Repeated cultures of the conjunctival exudate yielded Staph. aureus and diphtheroid bacilli. Dark field examination of material from the various lesions at no time showed Spirochaeta pallida.

Although the rectal temperature was only 99 F. on admission, it soon rose to 102.4 F. and fluctuated between 100 and 103 F. during the first week. Thereafter it gradually returned to normal. By the third day her lesions had progressed and she had become acutely ill. Ulcerations developed in the mouth from burst vesicles, and thick, milky, viscid fluid drooled profusely from the grotesquely deformed lips (fig. 2) and threatened to choke the patient. Dysphagia became severe; swallowing provoked burning under the whole length of the sternum. The conjunctival exudate became thick, obscuring vision completely at times.

By the ninth day a pseudomembrane had formed over the palpebral conjunctivas. This could be peeled off intact, and it reformed repeatedly. The rash spread to involve large areas of her body and extremities. Many of the lesions were dark red papules, and others were vesicles, a few showing central umbilication. Coalescence of the lesions on the palms occurred, causing so much pain that for days her hands were useless. In short, all accessible areas of the body, including the vagina and vulva, became involved during the first week. During this period of progression, itching was intense, especially of the arms and hands.

Treatment consisted, as in case 1, of withdrawing administration of phenobarbital, forcing fluids and attempting to soothe the affected tissues and to prevent secondary infection. Gradually the patient responded. The lesions regressed, and large sheets of skin were cast off, especially from the palms. Finally the finger nails loosened and replacement began. After one month in the hospital, the patient was discharged to the care of the syphilis clinic, where after several weeks injections of clorarsen were resumed, with no untoward reaction. Two months after discharge the patient felt better than ever. There was minimal scarring of the conjunctivas and lips; fading pigmented areas marked the sites of the previous cutaneous lesions, and replacement of the nails was rapidly approaching completion.

Fig. 2 (case 2).—Note the swollen lips, the profuse oral discharge and the edematous, crusted eyelids.

COMMENT

Two general types of cutaneous reactions to phenobarbital are recognized: (1) a sensitization reaction, manifested chiefly by urticarial wheals and itching, and (2) a toxic reaction, characterized usually by a morbilliform or scarlatiniform maculopapular erythema, areas of which occasionally coalesce and progress to vesicular or bullous formations, with or without jaundice. The bullous lesions may contain hemorrhagic fluid, which eventuates in thick, black crusts when the

lesions burst.[2] The symptoms of acute poisoning, such as stupor, speech disorders, dilated pupils, nystagmus and ataxia, are generally noted following a single massive dose and are usually not encountered in persons with cutaneous reactions, and vice versa.[2] Neither of our patients had urticaria, and only 1 complained of itching. The eruption in each corresponded to the toxic type and was of the severe degree characterized by coalescence and bullous formation, although neither had jaundice and only 1 (case 1) showed any appreciable hemorrhagic crusting.

Patients with a rash, however, frequently have a fever, with a temperature which may reach 104 or 105 F., and with the more severe reactions there are associated stomatitis, pharyngitis and conjunctivitis.[6] The exudate may be so great that a pseudomembrane is formed, suggesting diphtheria.[5a] This was especially true of the conjunctival exudate in case 2, in which intact sheets of exudate could be peeled from the lids but no diphtheria bacilli were isolated. In this case there was also pain on swallowing, which probably indicated an esophagitis. The patient of Wile and Benson,[5a] who likewise had great difficulty in swallowing, was found at necropsy to have an acute diphtheritic esophagitis.

Exfoliation of the skin occurred in both of our cases, being most striking on the hands and feet, where bullae had been prominent, although fine, scaly desquamation was evident from the other cutaneous lesions. Neither patient lost any hair, as some have done,[2] yet each lost all her nails. Poole [7] reported the observations at necropsy in a case in which exfoliation also affected the bronchi, renal pelves and ureters. He suggested that the mechanism of death in exfoliative dermatitis might be bronchial obstruction, resulting from the shedding of the bronchial mucosa, and not primary bronchopneumonia. In this respect, Sexton, Pike and Nielson [8] reported postmortem observations in a case in which both lungs were moderately firm but not typical of pneumonic consolidation, contained a hemorrhagic, purulent exudate in the smaller bronchi and showed several small necrotic areas in the alveoli. Neither of our patients, however, despite having fever, showed any sign of bronchopneumonia, bronchial obstruction or any tendency toward renal insufficiency, as might be expected if exfoliation of the mucosa of the urinary tract occurred to an important degree.

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6. Haubrich, B. P.: Phenobarbital Poisoning, New England J. Med. **211**:264 (Aug. 9) 1934. Menninger.[2]

7. Poole, A. K.: Drug Reactions from Barbital and Phenobarbital, Yale J. Biol. & Med. **1**:345 (July) 1929.

8. Sexton, D. L.; Pike, G. M., and Nielson, A.: Exfoliative Dermatitis and Death Due to Phenobarbital, J. A. M. A. **116**:700 (Feb. 22) 1941.

It is worth repeating that phenobarbital is probably the most frequently prescribed sedative in modern medical practice [5a] and that, as Hambourger [9] has stated, over two million doses of barbiturates are sold daily in the United States. Even if the incidence of rashes is less than 5 per cent among persons taking phenobarbital and still less among those taking other barbiturates, nevertheless the absolute number of rashes due to the barbiturates in this country each year must be tremendous. Although Gillespie [10] concluded that no death has occurred, barring the fatal cutaneous reactions exhibited in rare cases of strong idiosyncrasy following the ingestion of single or repeated therapeutic doses, it is probable that many more serious reactions and deaths have occurred than have been recognized and recorded. Indeed, Scarlett and MacNab [8] were impressed by the increasing number of toxic reactions to the barbiturates in recent years and reported more than 50 cases of toxic reactions due to phenobarbital in their own practice during a four year period. This experience led them to curtail strictly their use of phenobarbital.

It may be objected that the diagnosis of dermatitis due to phenobarbital is difficult to prove. That is the probable reason that more cases have not been recognized. In our cases the diagnosis was based on circumstantial evidence. A patch test was tried in the first case, after the patient's recovery, but no reaction developed. Intracutaneous tests have been recommended [6]; an urticarial wheal develops quickly in sensitive patients. An intracutaneous test was tried on our first patient, with 0.2 cc. of a 1 per cent solution of soluble phenobarbital in physiologic solution of sodium chloride and with physiologic solution of sodium chloride as a control. There was no evidence of any reaction immediately or during the next forty-eight hours. Menninger [2] noted that readministration of phenobarbital orally has caused the rash to reappear in some patients but not in all, whereas others recovered from their rash while administration of the drug was continued, even in increased dosage. Because the evidence implicating phenobarbital in our cases seemed convincing and because the original reaction had been extraordinarily severe, we thought oral readministration of the drug inadvisable.

Clinically, the eruptions in our cases bore a striking resemblance to certain ones that have been labeled "atypical erythema exsudativum multiforme," [11] the cause of which has not been determined. Stevens

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9. Hambourger, W. E.: Study of Promiscuous Use of Barbiturates: Their Use in Suicides, J. A. M. A. **112**:1340 (April 8) 1939.

10. Gillespie, R. D.: On Alleged Dangers of Barbiturates, Lancet **1**:337 (Feb. 17) 1934.

11. Ginandes, G. J.: Eruptive Fever with Stomatitis and Ophthalmia, Am. J. Dis. Child. **49**:1148 (May) 1935.

and Johnson [12] described an eruptive fever with ophthalmia that caused blindness in 1 of their 2 patients. No history of drug ingestion was obtained, and they suggested that the condition was a hitherto unrecognized disease entity. Klauder [13] added 4 similar cases, in 1937, under the title of "Ectodermosis Erosiva Pluriorificialis" and suggested that the condition resembled hoof and mouth disease. Generally, these reports have stated that drugs were not responsible, although it is admitted that certain drugs will produce mucosal and cutaneous lesions. In fact, Ginandes [11] emphasized the possible causative role of phenylethylhydratoin, and Sutton and Sutton [14] suggested phenolphthalein as the responsible agent. Because the eruptions of our patients resembled closely those described by the authors mentioned, and because phenobarbital undoubtedly was the causative factor in our cases, we suggest that phenobarbital may well have been the causative factor in many of the recorded cases. A history of drug ingestion is frequently difficult to obtain, and the name of the drug used is even more difficult to ferret out.

SUMMARY

Two cases of severe toxic eruption following the use of phenobarbital are reported. Both patients recovered. In addition to the skin, all the mucosal surfaces, except those of the bronchial and urinary systems, were obviously affected. No obvious loss of hair occurred, but each eventually shed all finger and toe nails.

One patient (case 1) took a total dose of 1.53 Gm. of phenobarbital over a period of twenty days. The other patient (case 2) consumed 4.8 Gm. in thirty-nine days.

The salient points of chronic phenobarbital intoxication, as manifested by a cutaneous reaction, and the dangers attendant on the present promiscuous use of the barbiturate sedatives are briefly discussed.

The suggestion is offered that phenobarbital may well have been the causative agent in many of the cases recorded in the literature as instances of "atypical erythema exsudativum multiforme" of unknown cause. The cutaneous and mucosal eruptions in these cases resembled closely those seen in our cases.

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12. Stevens, A. M., and Johnson, F. C.: A New Eruptive Fever Associated with Stomatitis and Ophthalmia, Am. J. Dis. Child. **24**:506 (Dec.) 1922.

13. Klauder, J. V.: Ectodermosis Erosiva Pluriorificialis, Arch. Dermat. & Syph. **36**:1067 (Nov.) 1937.

14. Sutton, R. L., and Sutton, R. L., Jr.: Diseases of the Skin, ed. 10, St. Louis, C. V. Mosby Company, 1939, p. 252.

GRANULOMA ANNULARE

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This study is a review of 31 cases of granuloma annulare which were observed at the Mayo Clinic between 1916 and July 1941. The purpose of this review was twofold. First, thorough study was made of material obtained for biopsy in 13 cases of granuloma annulare, and in this study an attempt was made to determine the essential characteristics which are necessary to the making of a diagnosis. Second, by correlation and evaluation of the clinical observations in 31 cases and the results of histologic study in 13 cases, we hope to present evidence which will assist in determining the role played by tuberculosis in the causation of granuloma annulare.

HISTORICAL ASPECTS

It has been generally accepted that the credit for the first description of this cutaneous disease should be ascribed to Colcott Fox,[1] who, in 1895, reported a case of it under the name "ringed eruption on the fingers." The first case to be found in the dermatologic literature, however, is one which Crocker reported in 1894 as a case of lupus erythematosus resembling lichen planus.[2] After recognizing his error, in 1902 he proposed the name granuloma annulare for the disease.[3]

Although some authors[4] have considered erythema elevatum diutinum as described by Crocker and Williams[5] to be a variant of

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From the Section on Dermatology and Syphilology of the Mayo Clinic.

Abridgment of a thesis submitted by Dr. Prunty to the faculty of the Graduate School of the University of Minnesota in partial fulfilment of the requirements for the degree of Master of Science in Dermatology and Syphilology.

1. Fox, C.: Ringed Eruption on the Fingers, Brit. J. Dermat. **7**:91-92 (March) 1895.

2. Crocker, H. R.: Lupus Erythematosus as an Imitator of Various Forms of Dermatitis, J. Cutan. & Genito-Urin. Dis. **12**:1-9 (Jan.) 1894.

3. Crocker, H. R.: Granuloma Annulare, Brit. J. Dermat. **14**:1-9 (Jan.) 1902.

4. Galloway, J.: Lichen Annularis: A "Ringed Eruption" of the Extremities, Brit. J. Dermat. **11**:221-233 (June) 1899. Hartzell, M. B.: Diseases of the Skin, ed. 2, Philadelphia, J. B. Lippincott Company, 1919. Sweitzer, S. E.: Tuberculide en Plaque, Arch. Dermat. & Syph. **24**:842-850 (Nov.) 1931.

5. Crocker, H. R., and Williams, C.: Erythema Elevatum Diutinum, Brit. J. Dermat. **6**:1-9 (Jan.); 32-38 (Feb.) 1894.

granuloma annulare, others [6] have expressed the belief that it is a clinical and pathologic entity.

The controversy concerning the part played by tuberculosis in the pathogenesis of granuloma annulare was begun by those [7] who noted a histologic similarity between granuloma annulare and Boeck's sarcoid. Opposition to this view, however, was expressed by a number of authors.[8]

In the more recent literature most of the proponents of the tuberculous causation of granuloma annulare point to its similarity histologically to the tuberculids, especially the papulonecrotic tuberculids.[9]

Halliwell and Ingram,[10] in reviewing 252 cases of the disease reported in the literature, found associated tuberculosis in 24 and Boeck's sarcoid

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6. Templeton, H. J.: Erythema Elevatum Diutinum, Brit. J. Dermat. **40**:193-196 (May) 1928. Weber, F. P.: A Note on the Suggested Tuberculous Origin of Granuloma Annulare, ibid. **41**:67-68 (Feb.) 1929.

7. (*a*) Little, E. G.: Granuloma Annulare, Brit. J. Dermat. **20**:213-229 (July); 248-257 (Aug.); 281-296 (Sept.); 317-327 (Oct.) 1908. (*b*) Prunty, F. C.: Granuloma Annulare: A Clinical and Histopathological Study, Thesis, University of Minnesota Graduate School, 1941.

8. (*a*) Arndt, G.: Zur Kenntnis des Granuloma annulare (Radcliffe Crocker), Arch. f. Dermat. u. Syph. **108**:229-260, 1911. (*b*) Brun, A.: Ein Beitrag zur Kenntnis des Granuloma annulare (Radcliffe Crocker), ibid. **135**:117-132, 1921. (*c*) Hartzell, M. B.: Granuloma Annulare: A Report of Five Cases, J. A. M. A. **63**:230-232 (July 18) 1914. (*d*) Saenz, B., and Oteiza, A.: Algunas observationes sobre la etiologia del granuloma annular, Bull. Soc. cubana de dermat. **1**:12 (June) 1929.

9. (*a*) Goldschlag: Granuloma annulare, papulonekrotische Tuberkulide, Erythema induratum-ähnliche Veränderungen, Zentralbl. f. Haut- u. Geschlechtskr. **19**:609, 1926. (*b*) Gougerot and Bonnin: Granulome annulaire ou érythématosclérose circinée des mains à structure tuberculoïde. Discussion étiologique, Bull. Soc. franç. de dermat. et syph. **26**:50-56 (March) 1919. (*c*) Grütz, O., and Hornemann, E.: Beiträge zur Klinik und Histologie des Granuloma annulare, Arch. f. Dermat. u. Syph. **136**:1-11, 1921. (*d*) Lehner, E.: Granuloma annulare, Zentralbl. f. Haut- u. Geschlechtskr. **38**:36-37, 1931. (*e*) Milian, G., and Périn, L.: Granulome annulaire: lésions histologiques tuberculoïdes, Bull. Soc. franç. de dermat. et syph. **38**:776-779 (May) 1931. (*f*) Pinkus, H.: Ueber atypische Tuberkulide, zugleich ein Beitrag für Ätiologie des Granuloma annulare, Arch. f. Dermat. u. Syph. **170**:194-222, 1934. (*g*) Rostenberg, A., Jr., in discussion on Urmansky.[22b] (*h*) Schaumann, J.: Benign Lymphogranuloma and Its Cutaneous Manifestations, Brit. J. Dermat. **36**:515-544 (Dec.) 1924. (*i*) Stettler, E.: Beitrag zur Kenntnis des Granuloma annulare, Arch. f. Dermat. u. Syph. **132**:314-328, 1921. (*j*) Weidman, F. D., and Besancon, J. H.: Erythema Elevatum Diutinum: Rôle of Streptococci and Relationship to Other Rheumatic Dermatoses, Arch. Dermat. & Syph. **20**:593-619 (Nov.) 1929.

10. Halliwell, E. O., and Ingram, J. T.: Granuloma Annulare, Brit. J. Dermat. **47**:319-340 (Aug.-Sept.) 1935.

in 2. They concluded that granuloma annulare is a blood-borne toxic manifestation almost invariably arising in a tuberculous soil.

Michael [11] expressed the opinion that "Granuloma annulare is caused by tuberculosis in some cases: in others, an unknown infectious agent appears to be the cause." Other writers [12] have considered granuloma annulare to be a syndrome associated with various micro-organisms. Still others believe that the disease can be explained by Jadassohn's theory of positive energy [13] in regard to tuberculosis.[14]

Bugarski [15] concluded that the toxins of tuberculosis are photosensitizers and that when these are liberated on the skin, changes arise as immune products in the form of granuloma annulare.

On the other hand, several authorities do not consider that sufficient proof has been presented to permit classification of granuloma annulare as a tuberculid.[16]

The similarity, histologically, between granuloma annulare and necrobiosis lipoidica diabeticorum was first pointed out by Bernstein [17]

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11. Michael, J. C.: Etiology of Granuloma Annulare, with Special Reference to the Tuberculous Theory, Arch. Dermat. & Syph. **29**:189-205 (Feb.) 1934.

12. (*a*) Midana, A.: "Foci" e granuloma annulare, Dermosifilografo **13**:315-319, 1938; abstracted, Zentralbl. f. Haut- u. Geschlechtskr. **60**:131, 1938. (*b*) Nicolette, V.: Etiopatogenesi del granuloma anulare, Gior. ital. di dermat. e sif. **71**:1848, 1930; abstracted, Zentralbl. f. Haut- u. Geschlechtskr. **36**:800, 1931. (*c*) Rost, G. A.: Diagnose und Therapie der Hauttuberkulose in der Praxis, Leipzig, Johann Ambrosius Barth, 1930, p. 56.

13. (*a*) Martenstein, H., and Noll, R.: Statistische Untersuchungen über die Tuberkulinreaktion, Arch. f. Dermat. u. Syph. **158**:409-420, 1929. (*b*) Rasch, C., and Gregersen, F.: Ueber einen neuen Typus von sarkoiden Geschwülsten der Haut, ibid. **64**:337-345, 1903. (*c*) Wichmann, P.: Die Diagnose der Hauttuberkulose durch Vergleichung der im Krankheitsherd und Normalhaut angestellten Intrakutaninjektion, Dermat. Wchnschr. **65**:887-901 (Sept. 22) 1917.

14. Wolf, C., in discussion on Urmansky.[22b]

15. Bugarski, S.: Granuloma annulare mit besonderer Berücksichtigung der ätiologischen Frage dieser Erkrankung, Zentralbl. f. Haut- u. Geschlechtskr. **60**: 517-518, 1938.

16. (*a*) Boldt, A.: Beitrag zur Klinik und Ätiologie des Granuloma annulare, Arch. f. Dermat. u. Syph. **179**:603-610, 1939. (*b*) Gans, O.: Histologie der Hautkrankheiten, Berlin, Julius Springer, 1925, vol. 1. (*c*) Goodman, M. H., and Ketron, L. W.: Granuloma Annulare: Report of Unusual Cases with Comment on the Histology of the Disease, Arch. Dermat. & Syph. **33**:473-494 (March) 1936. (*d*) Jacobi, F., in Jadassohn, J.: Handbuch der Haut- und Geschlechtskrankheiten, Berlin, Julius Springer, 1931, vol. 10, pp. 796-822. (*e*) Kyrle, J.: Histo-Biologie der menschlichen Haut und ihrer Erkrankungen, ibid., 1927, vol. 2, pp. 191-193. (*f*) Michelson, H. E., in discussion on Michael.[11] (*g*) Montgomery, H.: Histopathology of Various Types of Cutaneous Tuberculosis, Arch. Dermat. & Syph. **35**:698-712 (April) 1937.

17. Bernstein, J. C.: Necrobiosis Lipoidica Diabeticorum (Urbach): Comparison with Granuloma Annulare, Arch. Dermat. & Syph. **36**:282-286 (Aug.) 1937.

and recently by Hildebrand, Rynearson and one of us [18] (Montgomery) and others.[19] Stillians [20] in 1919 reported "an unusual case of granuloma annulare" associated with diabetes mellitus in which he noted that results of staining frozen sections for fat were positive.

Although the clinical appearance of granuloma annulare is considered to be characteristic, a number of cases have been reported in which rather unusual variations in morphology were present.[21] Among those variations which may be noted are erythematous plaques [22] of various sizes of widely disseminated discrete papules [23] and subcutaneous lesions.[24]

CLINICAL STUDIES

The well known clinical picture of the usual lesion of granuloma annulare was described in detail by Little.[7a] All the lesions presented by the patients in our series were of the cutaneous type, and most of them had the typical appearance of granuloma annulare (fig. 1). In some cases, in addition to the annular lesion, small discrete nodules were seen. A few lesions had a plaquelike appearance, because of a confluence of nodules.

Of the 31 cases in this study, in only 10 was the condition limited to a single lesion. In 4 of these 10 the lesion was situated on a lower extremity, and in 6 it appeared on an upper extremity. In the other 21 cases, the lesions ranged in number from two to more than thirty. In 11 of these 21 cases, the lesions also were limited to the extremities; of the remaining 10 cases (in some of which lesions also were found on the extremities), in 2 there were lesions on the back, abdomen, buttocks and the face; in 1 there were lesions on the neck, and in another many lesions were distributed over the trunk and extremities.

In this study, an effort was made to determine the status of the general health of all patients at the time of their examination. Special

18. Hildebrand, A. G.; Montgomery, H., and Rynearson, E. H.: Necrobiosis Lipoidica Diabeticorum, Arch. Int. Med. **66**:851-878 (Oct.) 1940.

19. (*a*) Ellis, F. A.: Necrobiosis Lipoidica: A Form of Granuloma Annulare? Arch. Dermat. & Syph. **43**:822-828 (May) 1941. (*b*) Boldt.[16a]

20. Stillians, A. W.: An Unusual Case of Granuloma Annulare, J. Cutan. Dis. **37**:580-589 (Sept.) 1919.

21. Vignolo-Lutati, C.: Beitrag zum Stadium des sogenannten Granuloma annulare (R. Crocker), Dermat. Wchnschr. **54**:77 (Jan. 20) 1912.

22. (*a*) Gougerot, H., and Arnandet, cited by Goodman and Ketron.[16c] (*b*) Urmansky, M.: Granuloma Annulare: Case Report, Arch. Dermat. & Syph. **32**: 511 (Sept.) 1935. (*c*) Goodman and Ketron.[16c]

23. Monash, S.: Granuloma Annulare Disseminatum: Report of Two Cases, Arch. Dermat. & Syph. **25**:122-131 (Jan.) 1932.

24. Grauer, F. H.: Granuloma Annulare: Report of an Unusual Case, Arch. Dermat. & Syph. **30**:785-789 (Dec.) 1934. Jacobi.[16d]

attention was given to the history, both personal and familial, with reference to tuberculosis, rheumatism and diabetes mellitus.

Of the 31 patients studied, 12 were less than 10 years old. The youngest was 2 years old and the oldest was 57. The youngest age at which granuloma annulare had occurred was 1 year. The duration of the condition at the time of examination ranged from one month to fourteen years. Nineteen of the patients were female, and 12 were male.

Twenty-eight patients underwent roentgenologic examination of the thorax. One was reported as having calcified hilus glands. Twenty-seven were reported as having a normal thorax at the time of their first examination. One patient returned three years after such an examination and was found to have a healed lesion in the apex of the left lung. The reaction to the tuberculin test had changed from negative to positive during that time. However, there had been little change in the clinical

Fig. 1.—Typical lesion of granuloma annulare.

appearance of the lesions of granuloma annulare. Two patients said that pulmonary tuberculosis had been suspected prior to their examination at the clinic. No evidence to substantiate this diagnosis could be found. One patient reported having had uveitis nine months before granuloma annulare appeared. One patient had enlarged cervical lymph glands. Biopsy of one of these revealed tuberculosis.

One patient had had rheumatism three years prior to examination at the clinic, and another patient was complaining of aching in the legs, arms and shoulders at the time of examination. One patient had had pyelonephritis that had necessitated nephrectomy; this had been followed in a month by acute anterior poliomyelitis, and granuloma annulare had appeared two years later. No evidence of tuberculosis was found. One patient had chronic discoid lupus erythematosus of the face, which had been present for fifteen years, and granuloma annulare on the elbow,

which had been present for six months. One patient was known to have had mild diabetes mellitus for the three years prior to the time of examination. Another was found to have carcinoma of the breast, with metastasis to the axilla.

One tuberculin test [25] or more was performed on 15 patients. The majority of the tests were Mantoux in which 0.1 mg. of old tuberculin was used, but the purified protein derivative was used in the first and second strengths and the von Pirquet test was made in several cases in this series. Twelve of these 15 patients were less than 10 years of age. These tests were performed by physicians and technicians especially trained in such work. It is to be noted that negative reactions to tuberculin tests were obtained among all children at their first examination. One of the patients, as previously mentioned, exhibited a positive reaction to tuberculin on reexamination three years later. Of the 3 adult patients tested, 2 exhibited negative reactions, and 1 was reported to have exhibited a positive reaction when tested elsewhere.

Determinations of Lipids (Milligrams per Hundred Cubic Centimeters) in the Blood of Two Patients with Granuloma Annulare

Lipoid	Patient 1	Patient 2	Normal Values
Cholesterol	219	225	218
Cholesterol esters	124	167	154
Lecithin	480*	234	220
Fatty acids	270	264	350
Total lipoids	489	489	568

* There was not sufficient material on which this test could be repeated for verification.

For 2 patients, 9 and 11 years old, determinations of lipids in the blood were made, and the results appear in the accompanying table.

The course of the disease in 16 cases, as determined by subsequent examinations or follow-up letters, and the response to treatment were variable. It is probable that roentgen irradiation is the treatment of choice, but it is to be noted that some lesions cleared without any treatment and others cleared after they had been painted with tincture of iodine or after procaine hydrochloride had been injected beneath the lesion. In no case was there any evidence or history of residual scarring. In 1 case there was residual pigmentation.

HISTOLOGIC STUDIES

The following account of histologic alterations in the skin resulting from granuloma annulare is based on a study of material obtained for biopsy from 13 patients. Solution of formaldehyde was used as a

25. Sulzberger, M. B., and Wise, F.: Tuberculin: Newer Dermatological Considerations and Reasons for Its More General Use in Diagnosis, M. Clin. North America **14**:1555-1568 (May) 1931.

fixative in all cases, and in some of the cases fixation with alcohol also was carried out. The material was treated with the following stains: hematoxylin and eosin, Van Gieson's stain, elastin H, the Ziehl-Neelsen stain, mucicarmine and Galantha's mucin. In 2 cases sudan III also was used. The number of sections made in each case studied ranged from twenty to one hundred and ninety.

The detailed description of a representative case follows:

A white man 31 years old presented ringed nodular lesions on both elbows typical clinically of granuloma annulare. These had first appeared three years previous to his visit to the clinic and had been more noticeable in the summer. There was neither a personal nor a family history of tuberculosis or diabetes mellitus. Roentgenologic examination of the thorax revealed no evidence of tuberculosis. Reactions to serologic tests for syphilis were negative.

A specimen for biopsy was removed from a lesion on the patient's left elbow; the specimen was fixed in solution of formaldehyde and alcohol and stained by the aforementioned methods. The epidermis was thinned and exhibited some degree of flattening of the rete pegs. Just beneath the epidermis and separated from it by a thin area of apparently normal connective tissue was an irregular oblong zone of coagulation necrosis extending deep into the cutis. This zone was not strictly homogeneous but presented various stages of degeneration of connective tissue. There were a few strands of fairly normal-appearing connective tissue; others showed homogenization; some showed separation, fraying and fragmentation of the fibers, and still others exhibited complete granular degeneration. The elastic tissue in this zone of necrosis was fragmented but not destroyed. Surrounding this zone and producing a fairly well circumscribed nodule was a rather dense infiltrate composed of lymphocytes, fibroblasts and a few epithelioid cells in a radial arrangement. In and around this wall of infiltrate were dilated blood and lymph vessels which contained no other alterations. Traversing this region of infiltrate in a somewhat radial arrangement were several strands of apparently normal connective tissue. The elastic tissue, except where it was associated with bundles of connective tissue, was destroyed in the regions in which the infiltrate occurred. The vessels outside the wall of infiltrate revealed a perivascular lymphocytic infiltrate of moderate degree. The sweat glands also were surrounded by this type of infiltrate, but to a much less degree. Results of staining for fat were negative. Mycobacterium tuberculosis could not be demonstrated. Results of staining for mucin were positive.

This case presents the generally recognized typical histologic picture of granuloma annulare (fig. 2). A detailed account of the other 12 cases (in which material for biopsy was obtained) is not deemed necessary, but a summary of the pertinent observations made in these cases follows.

The epidermis was unaltered in 6 cases. In 3 cases there was slight thinning of the epidermis with some flattening of the rete pegs. In 4 others mild hyperkeratosis and acanthosis were present. Other alterations in the epidermis were not seen.

The papillary and subpapillary layers usually were normal. The elastic tissue in these regions was not altered, and there was at least a

thin layer of normal connective tissue separating the epidermis from the deeper nodule in all cases. In some cases there was moderate dilatation of the papillary vessels with mild perivascular lymphocytic infiltration. The endothelium of these vessels was unaltered.

The major histologic changes in this condition occur in the cutis, usually in the upper part of the cutis, but when nodules are large the full thickness of the cutis may be involved. The typical lesion consisted of a fairly well demarcated, round, oval or branched central zone of

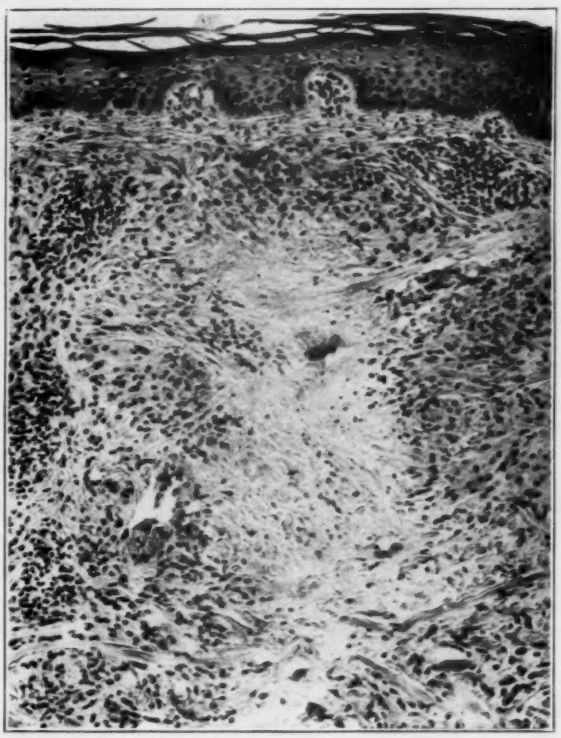

Fig. 2.—Typical picture of granuloma annulare, with degenerative changes in the connective tissue surrounded by lymphocytes, fibroblasts and epithelioid cells in radial arrangement (artefact in the center of the lesion; hematoxylin and eosin; × 85).

coagulation necrosis of the connective tissue, surrounded by an infiltrate of lymphocytes, fibroblasts and epithelioid cells in a radial arrangement. In and around this wall of infiltrate were numerous dilated but otherwise unaltered blood and lymph vessels. Sweat glands and blood vessels in the adjacent tissue frequently were surrounded by a similar cellular infiltrate. Except for certain variations, usually of degree rather than of structure, the histologic picture was fairly constant. Certain variants and their significance will be discussed in detail herein (fig. 3).

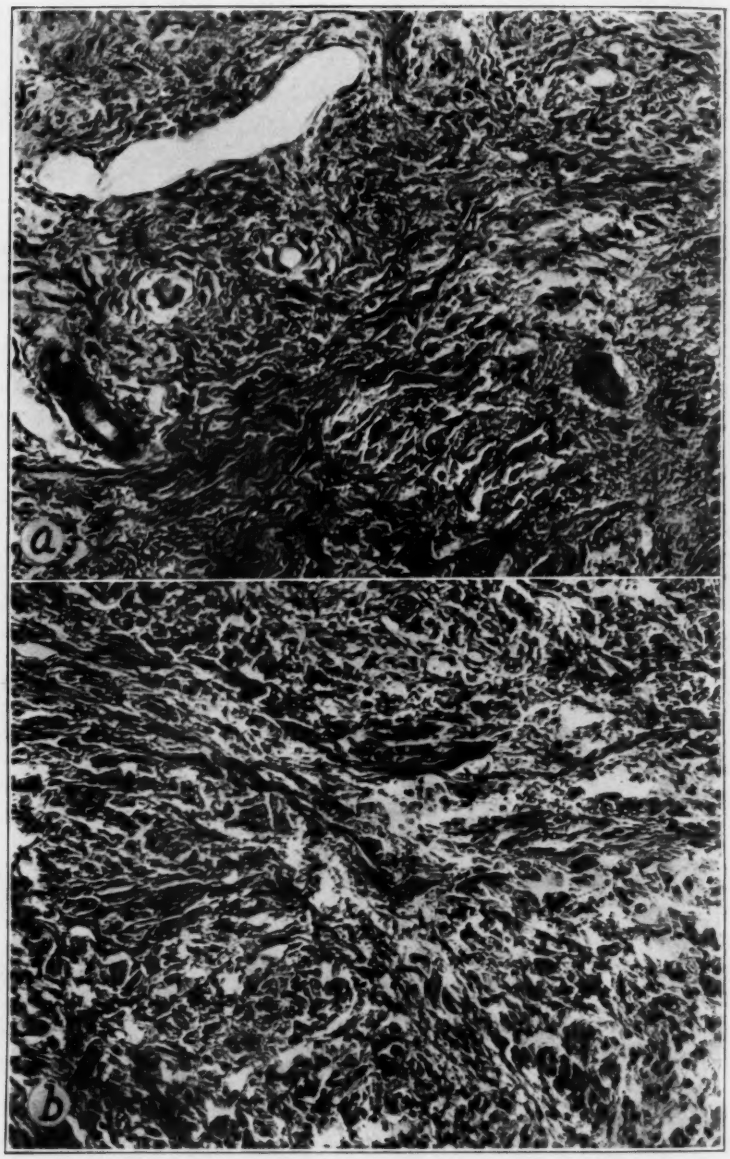

Fig. 3.—Early lesions of granuloma annulare, *a*, of four months' duration, showing beginning degeneration of connective tissue with radial arrangement of infiltrate and, *b*, showing foreign body type of giant cells (hematoxylin and eosin; × 185).

Biopsy of the lesions of the lowest age in the series, one of one month's duration and one of four months' duration (fig. 3 *a*), revealed rather dense typical cellular infiltrates in radial arrangements around well demarcated areas showing minimal degeneration of the connective tissue. Much of the connective tissue appeared to be unaltered. The affected collagen was seen in various stages of degeneration, ranging from mild homogenization, intercepted edema, fragmentation of collagen bundles, separation and fraying of the individual fibers to granular degeneration and complete loss of structure. A number of bundles of connective tissue extended into or traversed the surrounding infiltrate in somewhat radial arrangement, so that the impression was gained that the infiltrate had pushed in between the connective tissue, compressing it, in an effort to wall off the central degenerative process. A few fragmented elastic tissue fibers were seen to be scattered through the central zone and associated with the radiating bundles of connective tissue. In this case, although it was not true in all cases, there was greater destruction of elastic than of connective tissue. The reverse was true in most instances, especially in regard to the central zone. Usually the elastic tissue was destroyed at places in which the infiltrate was occurring, but occasionally a few fragmented fibers could be seen in this area.

Contrary to Rasch,[13b] we could see no evidence to indicate that any degree of infiltrate had been present in the center of the lesion preceding the so-called necrosis. An occasional lymphocyte and polymorphonuclear leukocyte, as well as a slight amount of nuclear debris, sometimes were seen (in the center of the lesion), but in no case was there marked cellular necrosis. Neither were giant cells seen in this part of the lesion.

The degrees of degeneration varied from those that have been described to almost complete destruction of the connective tissue. This degenerative change, however, did not seem to parallel the age of the lesion. This was brought out by study of material from a lesion of ten years' duration, in which considerable normal connective tissue was seen in the central zone.

Material taken for biopsy from two lesions which previously had received roentgen ray therapy was studied. One lesion had received a single treatment; two treatments had been administered to the other at six week intervals, the last treatment having been given five weeks before the time of biopsy. Both lesions were typical clinically. One had been situated on the inner surface of the knee of a 7 year old girl, who also had similar lesions on the dorsa of the hands. The other had arisen on the dorsal surface of the left foot of a 4 year old girl. Subsequent follow-up reports revealed that both lesions underwent involution within six months without further treatment. In the first

instance there were multiple irregular-shaped zones of necrosis not as sharply demarcated as in most cases. In these zones a considerable amount of normal connective tissue was noted. The wall of infiltrate, composed of distinct cell types and in most parts arranged radially in certain areas exhibited a decrease in density and in some places showed a break in the wall. In these portions normal connective and elastic tissue was seen. A number of the blood vessels, ordinarily seen in the area of infiltrate to be unaltered, exhibited obliterative changes. There

Fig. 4.—Granuloma annulare in the process of resolution after two roentgen ray treatments. Only small areas of degenerated connective tissue are seen; the arrangement of the cellular infiltrate is irregular, and the rearrangement of connective tissue has a more normal pattern (hematoxylin and eosin; × 70).

was also atrophy of the sweat glands of some degree. In the second of these cases in which roentgen ray treatment had been used there were greater variations from the so-called typical picture (fig. 4). In the cutis was a fairly well defined zone in which nests and strands of lymphocytes and epithelioid cells with few fibroblasts could be seen. Except around a few small foci of coagulation necrosis, the infiltrate was not arranged radially. There was mild homogenization of some of the connective tissue separating the clumps and strands of infiltrate,

but for the most part the connective tissue, as well as the elastic tissue, appeared to be normal. Several vessels exhibited intimal proliferation and a perivascular infiltrate of fixed tissue cells. Mucin was present, especially in the vicinity of vessels. Atrophy of the dermal appendages also had occurred in this case.

Considering the histologic picture presented and the fact that these lesions cleared relatively soon after specimens for biopsy were taken, it is evident that these particular lesions were in the process of involution. In the second of these 2 cases (in which the lesions had received roentgen ray treatment) the process was more advanced than in the first. From a study of these sections it appears that the process is one of absorption of the degenerated connective tissue and cellular infiltrate, obliteration of some of the newly formed vessels and a return of the normal relation between connective and elastic tissue. In no sections was there evidence of marked fibrosis or scar formation.

Atrophy of the dermal appendages was noted only in those sections of lesions that had received roentgen ray therapy. It is therefore supposed that these changes were due to the actinic effect of the rays. Proliferative changes in the blood vessels may have been due, at least in part, to the same cause.

Except in the 2 cases previously discussed, the cellular infiltrate and especially its radial arrangement around central areas showed little variation. An occasional polymorphonuclear leukocyte was seen in a few of the sections, and in some a few plasma cells could be demonstrated. In 4 of the 13 cases, giant cells of the foreign body type were noted (fig. 3 *b*). These were usually situated near the periphery of the infiltrate and not associated with any zone of necrosis.

In 2 cases a preponderance of lymphocytes over fibroblasts and only a scattering of epithelioid cells were evident. In 2 other cases a preponderance of epithelioid cells, some arranged in small clumps, was noted.

Throughout the cellular infiltrate in all cases were seen many dilated blood and lymph vessels. These vessels were so numerous in some sections that, contrary to some opinions, we believe many of them must have been newly formed vessels. Except in those cases in which the patients had received roentgen ray therapy, these vessels seldom exhibited intimal proliferation or other alterations. In 2 cases, however, deeper, larger vessels not associated with the lesion were affected by moderate intimal proliferation. In none of the sections studied was a vessel found in or immediately associated with the zone of necrosis. Likewise, except in a case to be described later, none of the sections displayed any evidence of the formation of true tubercles.

Staining for acid-fast organisms gave negative results in all cases. In 2 cases sections were stained for fat with sudan III stain. In neither case was there evidence of lipid deposits.

The presence of mucin, first noted by Rasch, but since then seldom mentioned in the literature, was readily demonstrated in all cases in which biopsy was done (fig. 5). This material, which stained red when the mucicarmine method was used, was most dense in the necrobiotic portions. It appeared in the form of fine threads and granular deposits. In some cases it was seen to be separating the frayed fibers of partially degenerated collagen. It was also seen outlining bundles of connective tissue, some of which extended through the wall of the infiltrate showing

Fig. 5.—Mucin, appearing black in the picture, in the form of strands and granules, separating the bundles and fibers of connective tissue, more prominent in zones of degenerating connective tissue (mucicarmine; × 100).

no, or only early, degenerative changes. Occasionally this material was seen outlining some of the vessels of the cutis. It was not seen to have a relation to the dermal appendages. Halliwell and Ingram emphasized the fact that edema was noted in all the 12 cases they studied. Studies for mucin were not reported by them.

In 1 case an unusual histologic picture was present, one which could lead to considerable conjecture (fig. 6). In the same section could be seen a lesion composed chiefly of epithelioid cells, typical of

sarcoid, and a necrobiotic lesion such as is found in granuloma annulare. The patient stated that he had had recurrent nodular and plaquelike lesions on the dorsa of the right middle and ring fingers for ten years. These lesions usually had been more noticeable when his general health

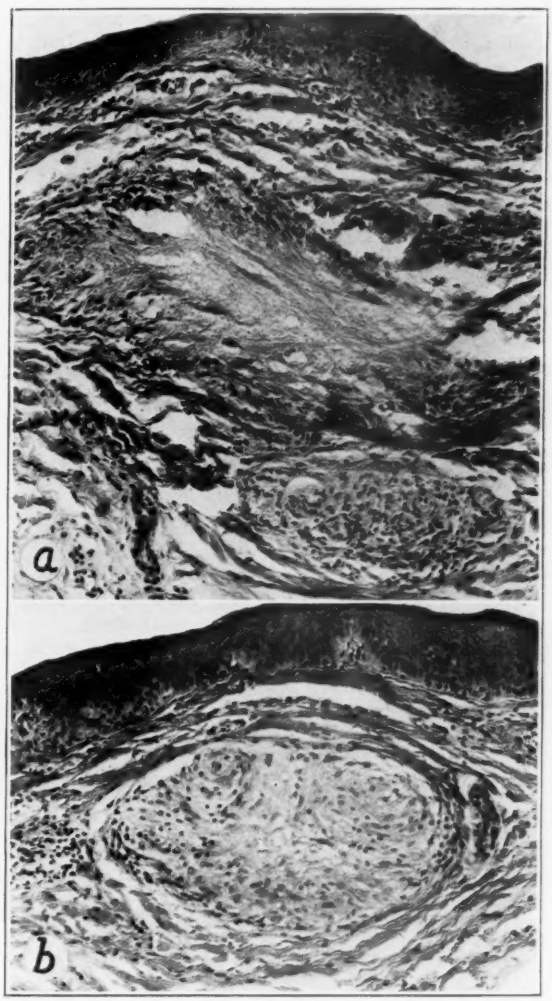

Fig. 6.—*a*, typical picture of granuloma annulare. Both *a* and *b* also show an epithelioid tubercle, suggestive of sarcoid (hematoxylin and eosin; × 100).

was comparatively poor. Four years previous to his admission to the clinic, glands in the right side of his neck had become enlarged. Later the enlargement had disappeared. Six months before his admission, the glands on the left side of his neck had become enlarged. On his

admission to the clinic, one of these glands was removed. The diagnosis of the pathologist was tuberculosis. Roentgenologic examination of the thorax revealed no demonstrable pathologic changes. The tissue in the section illustrated (fig. 6) was taken for biopsy from a lesion on the dorsum of the right middle finger. The central area of degeneration gave a strongly positive reaction when it was stained with mucicarmine.

This case, it seems to us, is of a special significance. In view of the fact that the patient was known to have tuberculosis, and in view of the histologic picture presented, we believe that a diagnosis of sarcoid must be made. The lesion (fig. 6*a*) in which central coagulation necrosis is seen, however, certainly does not belong in the category of sarcoid. It in no way resembles an epithelioid tubercle, and we have been unable to find in the literature any reference to this type or extent of necrosis in sarcoid. On the other hand, in none of the other cases of granuloma annulare studied was this picture of sarcoid in any way simulated. Occasionally, small clumps of epithelioid cells were seen, but in no case was a large epithelioid tubercle noted. Michelson wrote that it is a mistake to consider granuloma annulare as having fixed pathologic characteristics, for central necrosis is not always present and the early changes are rather nonspecific. It is evident, however, that the condition in this case cannot be explained on such a basis. Clinically, the lesions in this case were somewhat similar to those noted in the case of tuberculid en plaque described by Sweitzer; histologically, however, there were a dense infiltrate of lymphocytes, occasional giant cells and epithelioid tubercles but no caseation. Therefore, we believe that in our case two conditions were present: sarcoid and granuloma annulare. A somewhat similar circumstance was reported by Goeckerman and one of us (Montgomery) [26] in a case of discoid lupus erythematosus in which sarcoid was associated and in which there was a typical histologic picture of lupus erythematosus with an epithelioid tubercle deep in the cutis.

Assuming that both granuloma annulare and sarcoid were present in our case, it appears unlikely that two such dissimilar lesions could be produced in such close apposition by the same noxae. Although it is well known that more than one morphologic type of cutaneous tuberculosis may be present in the same person and that not infrequently the morphologic characteristics of a lesion may change, it does not seem likely that the reaction of the tissue to the same etiologic agent would produce two lesions in the same area, demonstrable at the same time, as dissimilar as the ones we have described.

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26. Goeckerman, W. H., and Montgomery, H.: Lupus Erythematosus: An Evaluation of Histopathologic Examinations, Arch. Dermat. & Syph. **25**:304-316 (Feb.) 1932.

DIAGNOSIS

Granuloma annulare in its typical form presents no diagnostic problem. The finding usually on the extremities but occasionally on other parts of the body of an annular lesion composed of small, somewhat translucent nodules with a central zone of normal skin is characteristic (fig. 1).

Excepting necrobiosis lipoidica diabeticorum, the varying lipoid disturbances are easily distinguished. The xanthomas are usually firm, yellowish, discrete nodules. Microscopic examination reveals intracellular deposits of lipids in foam cells. Lipoid proteinosis, an extracellular xanthomatosis, produces lesions which tend to form plaques and frequently involve the mucous membranes.

Necrobiosis lipoidica diabeticorum frequently simulates granuloma annulare microscopically and occasionally clinically (fig. 7). The diagnosis usually can be made clinically, however, by the finding on the lower extremities of nonelevated plaques with a reddish brown periphery and a yellowish center. It has been suggested that in some cases, to distinguish between the two conditions histologically, it is necessary to stain for fat, which is present extracellularly in necrobiosis lipoidica diabeticorum and which is absent in granuloma annulare.[16a]

On the other hand, Ellis [19a] recently reported a case in which positive results of staining for fats tended to confuse the issue rather than to assist in formation of the diagnosis. In his case lesions were present on the knee, ankle and dorsum of the hand which clinically had the appearance of granuloma annulare and which were said to have disappeared six months after examination. It was felt that the histologic picture was more suggestive of granuloma annulare than of necrobiosis lipoidica diabeticorum. The patient had severe uncontrolled diabetes, and results of staining for fat were positive. He suggested that necrobiosis lipoidica and granuloma annulare may be variants of the same disease.

We believe, however, that distinction of necrobiosis lipoidica diabeticorum usually can be made on the basis of the diffuse arrangement of the infiltrate, the intimal proliferation and obliteration of the vessels seen in this condition and the absence of mucin.

Granuloma annulare and lichen planus occasionally have been confused. When this occurs, microscopic examination usually settles the issue.

Erythema elevatum diutinum,[27] which until recent years had been considered to be a variant of granuloma annulare, is characterized by erythematous, elevated plaques, usually occurring at points of pressure. Frequently, a history of rheumatism can be elicited. Microscopically,

27. Trimble, W. B.: Erythema Elevatum Diutinum: Report of a Case with Comments on Its Nasologic Position, Arch. Dermat. & Syph. **13**:383-388 (March) 1926.

the epidermis exhibits acanthosis. In the cutis the changes consist of a perivascular infiltrate preponderantly polymorphonuclear in character, a decided hyaline degeneration of and surrounding the blood vessels and minimal necrosis. Occasionally a patient is seen who presents lesions which have the clinical features of erythema elevatum diutinum but which also have histologic features more suggestive of granuloma annulare than of the first-named condition. In one of Stillians' cases such a combination was presented.[28] The nodular type of granuloma

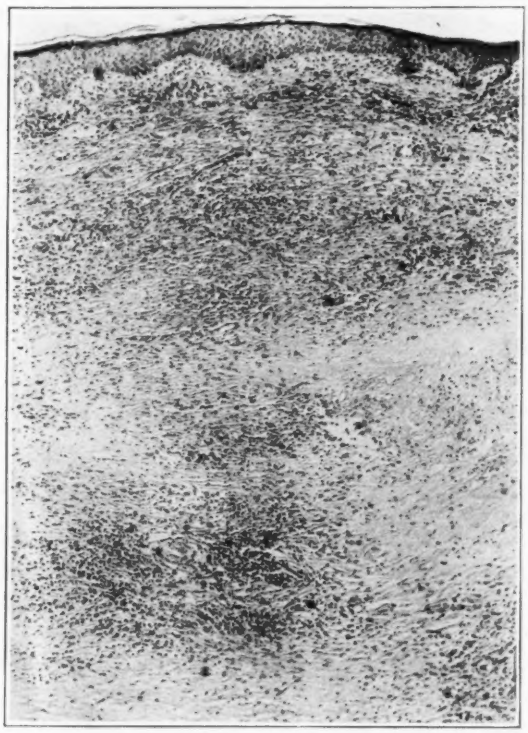

Fig. 7.—Necrobiosis lipoidica diabeticorum, with diffusely distributed infiltrate, giant cells, multiple foci of degenerative connective tissue and obliterative vascular changes (hematoxylin and eosin; × 60).

annulare may closely resemble erythema elevatum diutinum clinically, but histologically the two diseases are separate entities.

Rheumatic nodules, frequently found among children, may be distinguished by the concomitant observation of rheumatic fever, endocarditis or chorea and the association of the lesions with tendon sheaths, tendons or joints. Histologically, the picture is that of a vascular fibrous lesion.

28. Stillians, A. W.: Granuloma Annulare, J. Cutan. Dis. **37**:257 (April) 1919.

Annular sarcoid, which may resemble granuloma annulare clinically, can be diagnosed by the finding of nodules composed chiefly of epithelioid cells in a compact wall without radial arrangement and by the absence of coagulation necrosis of the connective tissue.

ETIOLOGIC CONSIDERATIONS

Clinical and laboratory evidence to support the theory of the tuberculous causation of granuloma annulare has, for the most part, been questionable. Dittrich [29] reported finding acid-fast organisms in sections taken from a lesion of granuloma annulare. Numerous other investigators, however, have been unable to confirm this observation. No acid-fast organisms were demonstrated in the 13 cases examined in this series. Jacobi [16d] stated that Volk reported a case of granuloma annulare with associated lesions of lupus vulgaris in which tuberculosis was demonstrated by inoculation of guinea pigs. The clinical and histologic descriptions of this case were brief. The question arises as to whether the condition present in Volk's case was granuloma annulare.

The results of testing with tuberculin can be evaluated only when the method used and the conditions under which the tests were performed are known.[25] It is felt that our series, although small, is of definite significance, especially since 12 of the patients were less than 10 years of age and all exhibited a negative reaction to tuberculin on their first examination. Myers and Harrington [30] made the following statements:

> The tuberculin test is the only fine screen available in the diagnosis of the first infection type of tuberculosis in children. It detects the presence of the disease long before other methods of examination are of any avail. . . . The tuberculin test gives no aid in the diagnosis of the reinfection type of tuberculosis. However, this type of disease develops only among positive tuberculin reactors, made so by previous first infection type of disease.

It has been shown recently that unless exposure to tuberculosis is continued, sensitiveness to tuberculin may diminish and in some cases be lost entirely. However, this is a gradual process. Lincoln, Raia and Gilbert [31] retested after intervals of from five to twelve years 113 children whose reactions had been positive; they found that for 111 of them the reaction remained positive. They found only 2 negative reactions among 352 children who had definite roentgenologic or clinical evidence of active or healed tuberculosis. They concluded that a negative reaction to the tuberculin test is of great significance in the exclusion

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29. Dittrich, O.: Zur Ätiologie des Granuloma annulare, Arch. f. Dermat. u. Syph. **153**:599-602, 1927.

30. Myers, J. A., and Harrington, F. E.: The Effect of Initial Tuberculosis Infection on Subsequent Tuberculous Lesions, J. A. M. A. **103**:1530-1535 (Nov. 17) 1934.

31. Lincoln, E. M.; Raia, A., and Gilbert, L. A.: Tuberculin Reactions in Children, J. Pediat. **12**:479-489 (April) 1938.

of tuberculosis among children and that the association of a negative reaction to the tuberculin test with a healed lesion is uncommon before a person is 12 years old.

In view of the work and opinions of these authorities and the negative reactions to tuberculin tests and the absence of any clinical or roentgenologic evidence of either active or healed tuberculosis in these 12 cases, we feel justified in stating that Mycobacterium tuberculosis had no part in the production of these lesions. Furthermore, the theory of positive anergy does not explain the negative reaction to tuberculin in these cases, because this theory presupposes a previous tuberculous infection. Although the same conclusions cannot be drawn from negative reactions to tuberculin in the older age group, the clinical evidence as a whole points against tuberculosis as an etiologic factor.

A number of writers have associated granuloma annulare with tuberculosis because they noted a histologic similarity between granuloma annulare and certain of the tuberculids. Jadassohn [32] referred to these as "transition forms," but Jacobi preferred to consider them as atypical tuberculids. In this study, excepting the case in which an associated sarcoid lesion was present, the histologic structure did not suggest tuberculosis. As has been pointed out, no formation of true tubercles was noted; the changes in vessels usually seen in tuberculosis were not observed, and in all cases the major changes appeared to be in the connective tissue.

Until further knowledge pertaining to the formation or deposition of mucin in the skin is obtained, no definite conclusions can be drawn concerning the etiologic significance of its presence in granuloma annulare. Except for the 1 case in which associated diabetes mellitus was present, there was no clinical or laboratory evidence to show the presence of an endocrine or metabolic disturbance in the cases of this series.

SUMMARY

This study consists of a review of 31 cases of granuloma annulare observed at the Mayo Clinic between 1916 and 1941. In 13 of these cases biopsy was performed.

A thorough review of the literature was made with special reference to histologic and etiologic aspects. This revealed the fact that although granuloma annulare is frequently referred to as a condition in which a typical histologic picture is presented, such a view is not concurred in by all writers. The cause of the disease is not known. The literature reveals a fairly even division of opinion concerning the role of tuberculosis in granuloma annulare.

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32. Jadassohn, J.: Remarks on Tuberculin in Dermatology, Brit. J. Dermat. **41**:451-472 (Dec.) 1929.

In clinical studies an effort was made to determine the status of the general health of the patients, with special reference to tuberculosis. Roentgenologic examination of the thorax of 28 patients was carried out, with negative results in 27. One patient had calcified hilus glands. In 1 case tuberculosis of the cervical glands was demonstrated.

Reactions to the tuberculin tests were negative for 14 patients at the time of their first examination at the clinic. Two of these patients were adults, and 12 were less than 10 years old. One of the latter group, on later examination, was found to have a healed apical lesion and a positive reaction to the tuberculin test. A third adult person was reported to have had a positive reaction to a tuberculin test performed elsewhere.

Study of the material obtained for biopsy in 13 cases disclosed only slight alterations in the epidermis. The major changes, occurring in the cutis, consisted of an infiltrate of lymphocytes, fibroblasts and epithelioid cells in a radial arrangement around a zone of myxomatous degeneration. These lesions, usually relatively large, were round, oval or branched and usually were fairly well demarcated. Varying degrees of degeneration of connective tissue were noted. The elastic tissue was not proportionately involved. Changes in vessels were minimal. A substance giving a positive reaction to stains for mucin was demonstrated in all cases. This substance was dense in many sections and was easily seen in all. This material was not seen in sections of tissue affected by necrobiosis lipoidica diabeticorum stained in the same manner. In 1 case lesions typical of granuloma annulare and sarcoid were seen in the same section. Staining for acid-fast organisms gave negative results in all cases.

An evaluation of the clinical and histologic data, in the light of present day knowledge concerning tuberculosis, especially among children, offers strong evidence against the concept that Myco. tuberculosis is an etiologic factor in granuloma annulare.

CONCLUSIONS

On the basis of the material presented we believe the following conclusions are justified.

Granuloma annulare is a benign, chronic, cutaneous disease of unknown cause which has not been proved to be associated with any systemic disease. It usually presents a typical clinical and histologic picture. Special staining for mucin gives a positive reaction in granuloma annulare. The etiologic significance of this observation is not known. However, it serves as an aid in diagnosis. Tuberculosis was not an etiologic factor in the cases of this series. The response to treatment is variable. Granuloma annulare usually undergoes involution without sequelae.

ATROPHY OF THE SKIN AND SUBCUTANEOUS FAT

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We have observed a patient with an unusual type of atrophy, which affected the skin and the subcutaneous tissue. The appearance was so bizarre and extensive as to be worthy of special notice.

REPORT OF A CASE

M. C., a white Slavish laborer aged 46, was first seen on Nov. 14, 1941, because of an extensive and severe atrophy of five years' duration.

This process began as a small circumscribed vesicular eruption of the dorsa of the feet, which within four months developed into an extensive dermatitis of the lower extremities, including the feet. The swelling, redness, itching and burning persisted for approximately two years. When this acute acrodermatitis subsided an atrophy of the skin and subcutaneous tissues became apparent.

These atrophic changes involved various parts of the body, and the involvement varied greatly in kind and in severity. On the knuckles but principally on the elbows the skin was thinned, wrinkled, inelastic and somewhat reddened, more so on the right than on the left elbow. A few venules and telangiectases were present. The dermatitis extended along the ulnar surface of the arm. It resembled poikiloderma in all respects except that pigmentation was lacking.

On the back of the torso and on the glans penis there were a number of rounded thumb nail–sized and even larger areas of atrophy. Umbilication was present in all of those of the torso; and to all intents and purposes the lesions were examples of anetoderma of Schweninger and Buzzi, while those on the glans penis were typical examples of anetoderma of Jadassohn.

The most noticeable changes of the skin were found on the lower extremities, beginning at the buttocks. Atrophy of the skin and subcutaneous tissues and a deep, dark acrocyanosis featured these changes; they were more extensive on the left side. On the left buttock the skin and subcutaneous tissue shrank into folds. The wrinkling emphasized the loss of elasticity of the skin and gave this area the appearance of accordion pleating. The atrophy of the skin from the knees downward was that seen in ordinary acrodermatitis atrophicans chronica. The skin was thin, scaly and cyanotic. A few tortuous veins were present on the very top of the horny layer.

The feet, especially the left one, showed great changes, chiefly because of loss of subcutaneous tissue, leaving the skin in folds. The inelastic atrophied skin appeared as a bag which was too roomy for what it contained, resulting in a moccasin-like

From the Pittsburgh Skin and Cancer Foundation.

deformity. The lack of fat caused pain on standing or walking (he described the sensation as that of walking on an exposed bone). The loss of tendon attachment of the small toe of the left foot permitted this digit to override the dorsum of the foot in a peculiar transverse fashion.

The nails also showed trophic alterations, and, paradoxically, the nails of the right foot were affected more adversely than those of the left foot (with the exception of the nail of the small left toe, which was completely absorbed). All of the nails had lost their transparency, and the nail substance was heaped up, nonadhesive and laminated.

There was a noticeable difference in the temperature of the two legs, the left being much colder.

The report of the neurologic consultation by Dr. George J. Wright and Dr. John A. Malcolm follows in part: "We will not describe to you the details of

Fig. 1.—Anetoderma of Jadassohn affecting the glans penis.

the dermatologic condition beyond saying that there seems to be an atrophied process involving not only the skin but the subcutaneous tissues. Both legs are involved, the left more than the right, but there is some suspicion of trouble in the upper extremities, especially over the knuckles and the elbows. The condition is painless, although associated with some itching. There are no sensory changes, except possibly some hyperalgesia to pinprick, which, of course, is easy to understand. There is no atrophy of muscles, no loss of power and no disturbance of the reflexes. Deep forms of sensibility, particularly postural and vibratory sensation, are intact. The more general neurologic examination, which includes a study of the cranial nerves, showed nothing.

"It would seem likely that the nervous system is involved, especially those parts that are concerned with nutrition, and in this particular instance, because

of the selectiveness of the distribution to the skin only, we are assuming and believing that the trouble has its origin in the autonomic nervous system."

The results of all the serologic tests for syphilis (Wassermann, Kahn and Hinton) were negative.

The blood count, including the differential count, and the urine were normal. The cholesterol content of the blood was 216 mg. per hundred cubic centimeters. The basal metabolic rate was —6 per cent.

The following results of roentgen ray examination were reported by Dr. F. L. Schumacher: The skull was unusually large, but there was no particular change

Fig. 2.—Accordion-pleating-like deformity of the left buttock. Note the small rounded areas of atrophy (Schweninger and Buzzi).

in the shape or texture of the bones. The sella was of the circular type, with unusually large clinoid processes and a smooth floor. There was no evidence of erosion. All other bones appeared normal except for a small cystic area in the proximal end of the middle phalanx of the second metacarpus.

The microscopic examination of sections of the skin from the back, the buttocks and the left leg showed the picture of acrodermatitis atrophicans chronica.

Thus, the atrophic changes presented may be classified under four headings: (1) acrodermatitis atrophicans chronica, (2) anetoderma of Jadassohn, (3) anetoderma of Schweninger and Buzzi and (4) a subcutaneous atrophy. The sub-

Fig. 3.—Loss of elasticity, especially of the left foot.

Fig. 4.—Moccasin type of deformity of the left foot.

cutaneous atrophy of the left buttock and left foot was so extensive that gross deformity and impairment in function resulted.

The neurologic report indicated that the trouble had its origin in the autonomic nerves, especially in that part which is concerned in nutrition. The changes in the nails, the result of this nutritional disturbance, were evident and instructive.

Fig. 5.—Acrodermatitis atrophicans chronica. Note the position of the left small toe.

COMMENT

The finding of the various types of atrophy in one patient raises the question whether these atrophic processes are specific entities. In this particular patient it seems that the same etiologic factor was capable of causing all of them.

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EPIDERMOLYSIS BULLOSA HEREDITARIA

REPORT OF TWO CASES WITH EXTENSIVE FAMILY HISTORIES

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The following cases of epidermolysis bullosa hereditaria are reported because:

1. This disease is rare.[1]

2. In these cases it was mild and abortive and there were interesting pedigrees.

3. In 1 case (case 1) the true diagnosis was missed for twenty-three years and the disease was repeatedly mistaken for a banal condition.

4. This disease is significant for military medicine because it is disabling even when mild.

CASE 1.—*History.*—J. W. G., 23 years old, a seaman, second class, United States Navy, was admitted to the dermatologic service of the United States Naval Hospital, Brooklyn, on Aug. 21, 1941, with the complaint of recurrent blistering of the feet of lifelong duration. The diagnosis on admission was fungous infection of the feet. The diagnosis of epidermolysis bullosa hereditaria was made first by Lieut. Comdr. M. B. Sulzberger. All historical data, except that of the complaint and its family trend, were irrelevant. The results of routine physical examination, except for that of the skin, were normal.

The patient stated that as long as he could remember he had had attacks of blisters, often on the feet, occasionally on the hands and rarely on other sites, such as the calves, inner surfaces of the thighs and buttocks. The episodes varied in severity and were always worse in the summer and during warm spells in the winter. The patient's home was in the South (Alabama), and most of his life was passed there. On some occasions the attacks were severe enough to disable him for a short time. The patient himself noted that an amount of trauma that did not affect other persons engaged in the same activity affected him with the blistering reaction. Such activities were playing football, riding horse, hunting in high boots, walking and marching as in military duty. The sites of the epidermo-

1. The following references contain cases with similar pedigrees: Haldane, J. B. S., and Poole, R.: A New Pedigree of Recurrent Bullous Eruption of the Feet, J. Hered. **33**:17, 1942. Cockayne, E. A.: Recurrent and Bullous Eruption of the Feet, Brit. J. Dermat. **50**:358, 1938.

lytic reaction were those undergoing pressure or friction, namely, the hands, feet, calves, inner surfaces of the thighs and buttocks.

Physical Examination.—On admission, examination of the skin showed several fresh and old bullae on the feet. These were situated at points of pressure, namely, on the heels, over the great toes, on the balls of the feet and over prominent tendinous lines on the dorsa of the feet. On the left heel there was a half-dollar-sized bulla. With rest in bed the bullae healed readily and uneventfully. When even restricted ambulation in the ward was resumed, small new lesions tended to appear. Examination of the skin on discharge showed healed and healing bullous lesions on the affected sites. Where the lesions were small at the outset, involution was complete with practically no scarring and only faint pigmentation. Where

Fig. 1.—Epidermolysis bullosa hereditaria.

there were larger blisters, the edges still showed some exfoliation. In two places, on one toe and over a prominent tendon, small vesicles were forming.

Family History.—The familial incidence of the condition in this case is known to the patient as far back as the third antecedent generation and down to the first generation after him. The genetic descent of the disease is graphically illustrated in figure 4. As may be seen, the paternal grandfather had the disease. In the next generation, three out of five children, that is, the patient's father and two paternal aunts, but not two paternal uncles, were affected. Of the patient's generation, he and three sisters, but not three brothers, were sufferers, as were three cousins by one of the affected aunts and one other cousin out of two children of the other affected aunt. None of the issue of the two unaffected uncles exhibited the

disease. In the last generation, none of the progeny of the patient's unaffected brothers showed the disease, but among nine children of two of the patient's affected sisters, four were affected and five were free of the disease.

CASE 2.—*History.*—T. H., a boy of 2 years, was seen in the private practice of Dr. M. B. Sulzberger and one of us (R. L. B.) on Oct. 1, 1941 for blisters of the left foot of six months' duration.

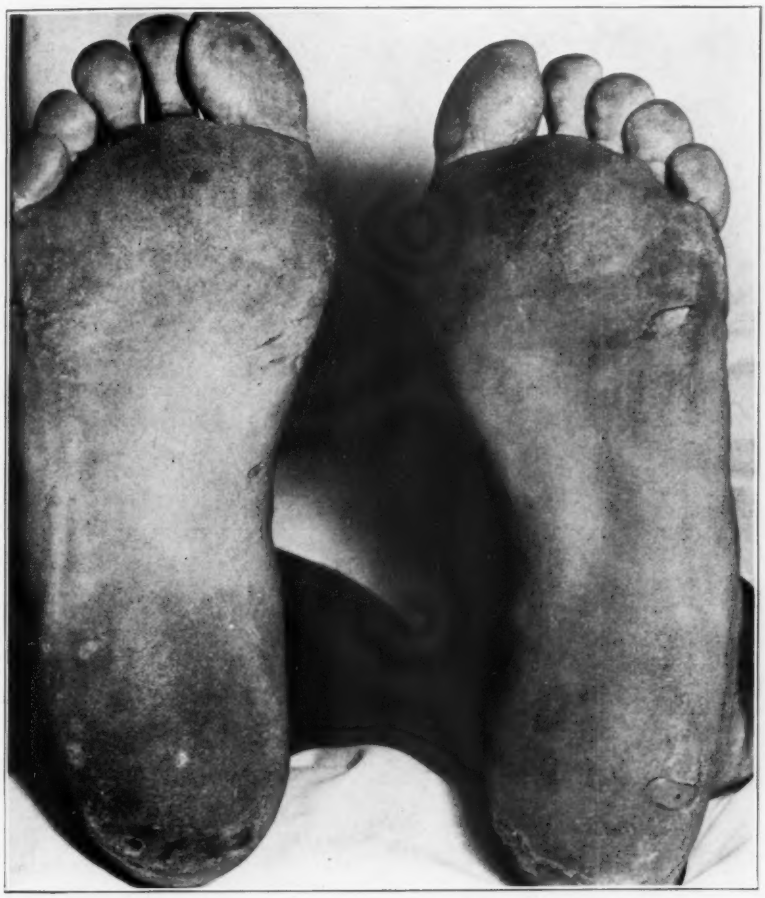

Fig. 2.—Epidermolysis bullosa hereditaria.

His parents stated that blisters developed on his left foot as soon as he began to walk. The boy's general health was excellent except for an atopic dermatitis (disseminated neurodermatitis), which appeared in the cubital and popliteal spaces off and on.

Physical Examination.—Near the base of the fourth left toenail there were four small vesicles.

Fig. 3.—Epidermolysis bullosa hereditaria.

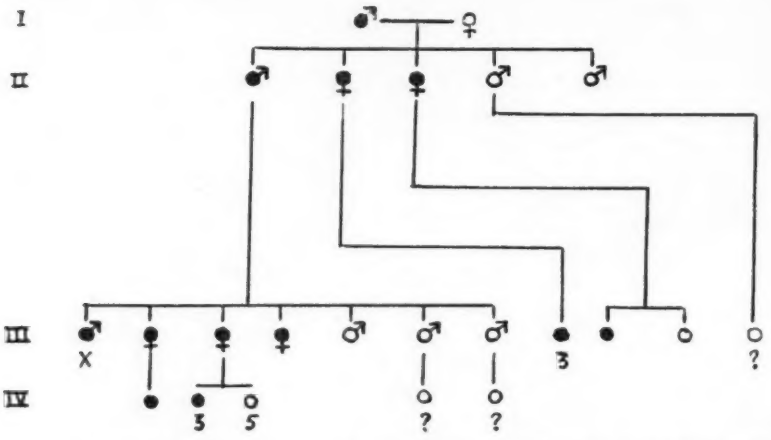

Fig. 4 (case 1).—Familial incidence of epidermolysis bullosa hereditaria. Filled-in symbols indicate affected persons; not filled-in symbols, unaffected persons. Symbol O (filled in or not filled in) indicates persons whose sex was not determined. Arabic numerals indicate the number of persons; the question mark indicates that the number of persons is unknown. Roman numerals indicate the generation. X indicates the patient.

Family History.—The familial incidence in this case is known as far back as the fourth antecedent generation. The genetic tree is shown in figure 5. The paternal great grandmother was a sufferer. In the next generation, one out of four children, i. e., the patient's paternal grandfather, had the disease. He was mildly afflicted at the age of 21 years, severely between 25 and 28 years of age and negligibly so thereafter. Here, too, long marches and summer weather were recalled as precipitating circumstances. In the father's generation, only one out of eight children of assorted parentage, namely, the patient's father, was affected. He exhibited the condition on the hands and feet, especially in the summer and almost not at all in the winter. In the patient's generation, he as an only child of his afflicted father, showed the disease, whereas children of an unaffected uncle and cousin were free of it.

In the opinion of Dr. Nathan Kaliss,[2] geneticist, department of pathology, Cornell University Medical College, these pedigrees indicate dominant transmission, possibly through a single pair of genes. There is no sex linkage. The segregation ratio expected in such cases is 1 : 1,

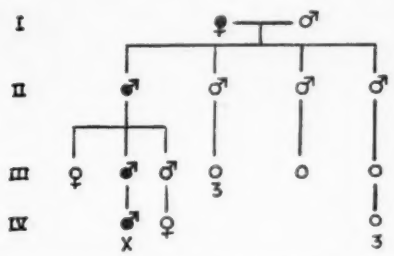

Fig. 5 (case 2).—Familial incidence of epidermolysis bullosa hereditaria. Filled-in symbols indicate affected persons; not filled-in symbols, unaffected persons. Symbol O (filled in or not filled in) indicates persons whose sex was not determined. Arabic numerals indicate the number of persons; the question mark indicates that the number of persons is unknown. Roman numerals indicate the generation. X indicates the patient.

and in one of our cases the ratio is 15 : 11, which is close correspondence. In neither case, nor combined, is the number of persons involved sufficient to illustrate this point perfectly.[3]

SUMMARY AND CONCLUSIONS

The cases herein reported are instances of a hereditary disease of the skin which is rare and results in a blistering reaction provoked by average pressure and friction to the skin.

2. Personal communication to the authors.

3. Cockayne, E. A.: Inherited Abnormalities of the Skin and Its Appendages, New York, Oxford University Press, 1933.

In 1 case the condition was improperly diagnosed for twenty-three years. The usual diagnoses were fungous infection and eczema. The abortive nature and the rarity of this disease caused it to be confused constantly with banal conditions by nondermatologic examiners.

The pedigrees are extensive and genetically informative.

The military importance of this disease lies in its incapacitation of the afflicted person for military service. Consequently, the medical officer, examining for recruitment or enlistment, should attempt to discover this rare dermatologic entity by a few pointed questions as to similar family occurrence. In this manner he may pick up even the mild condition which resembles the common vesicular and bullous dermatoses so much.

CUTANEOUS SENSITIVITY TO MERTHIOLATE AND OTHER MERCURIAL COMPOUNDS

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Some investigators claim that if a patient's skin is sensitive to one of the mercurials he may be sensitive to any compound containing mercury. We have investigated 5 patients with dermatitis due to merthiolate and found that 4 were sensitive to merthiolate and not to any other organic or inorganic mercury compounds with which they were tested.

Gross [1] reported on a patient who was sensitive to mercurophen (sodium hydroxymercury orthonitrophenolate). The patient was sensitive also to tincture of metaphen, 2 per cent yellow mercuric oxide ointment, 1:10,000 solution of mercury bichloride and 3 per cent mercurous chloride ointment but reacted negatively to patch tests with tincture of merthiolate and mercurochrome. Butterworth, discussing Gross's case, described a patient who was sensitive to 3 per cent ammoniated mercury ointment but not to 1:150 solution of mercurophen. Traub and Holmes [2] reported on a patient with dermatitis and stomatitis due to mercury amalgam fillings in whom positive reactions were elicited with ammoniated mercury ointment and solutions of mercurochrome and of mercury bichloride. Blumenthal and Jaffé [3] stated that the sensitivity to mercury as determined by patch tests depends on the relative solubility of the chemicals rather than on the complexity of the compounds. Wilson [4] observed a patient who was sensitive to hydrophen (orthophenylphenolmercuric nitrate) ointment. He was

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1. Gross, E. R.: Dermatitis Venenata (Mercury and Its Salts), Arch. Dermat. & Syph. **37**:689 (April) 1938.

2. Traub, E. F., and Holmes, R. H.: Dermatitis and Stomatitis from the Mercury of Amalgam Fillings, Arch. Dermat. & Syph. **38**:349 (Sept.) 1938.

3. Blumenthal, F., and Jaffé, K.: Zur Frage der Quecksilberüberempfindlichkeit, Dermat. Wchnschr. **91**:1668 (Nov. 8) 1930.

4. Wilson, D. J.: Eruption Due to Hydrophen Ointment: Case Report, Nebraska M. J. **24**:70 (Feb.) 1939.

sensitive also to mercury bichloride, mercurochrome, ammoniated mercury and phenylmercuric nitrate. Kesten [5] reported a case of conjunctivitis due to yellow mercuric oxide, and, although the patient was sensitive to a number of organic mercurials, he was most sensitive to the yellow mercuric oxide. Belote and Marshall [6] reported 2 cases of dermatitis due to metaphen. One of their patients was also sensitive to solution of mercury bichloride and 1 per cent solution of mercurochrome. They obtained many positive passive transfers in 16 normal patients when the material was applied by patch tests, whereas no positive reactions resulted from the topical application of the chemicals. Schwartz and Tulipan [7] stated that iodine definitely increases a person's sensitivity to ammoniated mercury. Gaumond [8] reported 2 cases of mercurial dermatitis; one patient apparently was sensitive to several organic mercurial compounds. Hawkins [9] observed a 7 year old boy who was sensitive to mercurochrome and to ammoniated mercury ointment, but tests on his mucous membrane gave negative results. Lawrence and Strauss [10] reported on a patient who showed a slightly positive reaction to 1 per cent mercury bichloride, a doubtful reaction to 1 per cent mercurochrome and to 1 per cent merthiolate and a rather severe reaction to 0.5 per cent tincture of metaphen and to 1 per cent potassium mercuric iodide but a negative reaction to 10 per cent ammoniated mercury ointment. Sulzberger [11] cited the case of a patient who was so sensitive to mercury that after he had spent one hour in a room in which a small quantity of mercurochrome had been spilled on the floor prior to his arrival, the following day a severe and protracted attack of generalized dermatitis developed accompanied by high temperature and enlarged lymph nodes. Sulzberger found that in performing routine patch tests with 10 per cent ammoniated mercury ointment and 10 per cent salicylic acid ointment he obtained relatively few positive reactions; but if the two ointments were combined so that the concentration was 5 per cent of each, then 50 per cent of all patients tested gave positive reactions.

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5. Kesten, B. M.: Conjunctivitis and Blepharitis Due to Yellow Mercuric Oxide, Arch. Ophth. **6**:582 (Oct.) 1931.

6. Belote, G. H., and Marshall, D.: Metaphen Dermatitis: Report of Two Cases, J. Michigan M. Soc. **34**:172 (March) 1935.

7. Schwartz, L., and Tulipan, L.: Occupational Diseases of the Skin, Philadelphia, Lea & Febiger, 1939, p. 140.

8. Gaumond, E.: Dermites mercurielles, Laval méd. **3**:171 (May) 1938.

9. Hawkins, H. F.: Mercurial Skin Sensitization, Dallas M. J. **20**:105 (Nov.) 1934.

10. Lawrence, J., and Strauss, M. J.: Dermatitis Due to Potassium Mercuric Iodide, Arch. Dermat. & Syph. **30**:76 (July) 1934.

11. Sulzberger, M.: Dermatologic Allergy, Springfield, Ill., Charles C. Thomas, Publisher, 1940, p. 92.

Pascher and Silverberg [12] reported on 5 patients with hypersensitivity to mercurochrome. Each patient was also sensitive to an inorganic mercurial, such as ammoniated mercury or mercury bichloride. In their fifth case parallel quantitative reactions were obtained to varying dilutions of mercurochrome and mercury bichloride. This might be interpreted to suggest that the reaction depended on the amount of mercury present. This is unlikely, as the mercury of the inorganic mercurials dissociates readily while the mercury of mercurochrome does not dissociate at all. Pascher and Silverberg stated that of all the mercurial preparations mercurochrome is one of the least likely to cause a dermatitis.

Sulzberger [13] suggested "that the patients who reacted to an organic mercurial might have failed to react to other mercurials not because they were not sensitive to the mercury but because other preparations delivered less free or dissociated mercury ions than the one to which the reaction was obtained." Krantz [13a] bubbled hydrogen sulfide through solutions of mercurochrome and merthiolate without producing any precipitate. This demonstrated that free mercury ions were not present in the solutions.

These reports suggest that if a person is sensitive to one of the mercury compounds, he may be sensitive to a number of them but not to all organic and inorganic mercurials.

Reimann [14] found that when he used thiocresol in concentrations stronger than 0.25 per cent a vesicular eruption occurred in a certain percentage of persons. Marks, Powell and Jamieson [15] stated:

> Since merthiolate is a derivative of a thio compound, the occasional erythema noted in a few highly sensitive persons following the use of unstabilized aqueous merthiolate solution may in part be attributable to this factor. . . . By rather simple stabilization methods applied to the solvent, merthiolate solution can be so prepared that it may be applied in 1 : 1000 dilution as wet dressings for twenty-four hours or longer without causing irritation in highly sensitive individuals who previously reacted after one minute exposure to the unmodified solution. Such stabilized merthiolate solutions retain their healing properties. The merthiolate solutions used in the work reported in this paper included stabilized solutions which cause no irritation in either ordinary or hypersensitive subjects.

These authors apparently used the terms "highly sensitive" and "hypersensitive" to designate persons whose skins are more easily affected by external irritants than the skin of the average person. They

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12. Pascher, F., and Silverberg, M. G.: Hypersensitivity to Mercurochrome Shown by the Patch Test, Arch. Dermat. & Syph. **27**:408 (March) 1933.

13. Sulzberger, M.: Personal communication to the authors.

13a. Krantz, J. C.: Personal communication to the authors.

14. Reimann, S. P.: Thiocresol in Wound Healing, Ann. Surg. **93**:624 (Feb.) 1931.

15. Marks, H. H.; Powell, H. M., and Jamieson, W. A.: Merthiolate as a Skin Disinfecting Agent, J. Lab. & Clin. Med. **17**:443 (Feb.) 1932.

could not have included under these terms the sensitized or allergically altered skin which the term hypersensitive usually implies.

H. M. Robinson Sr.[16] in 1937 reported a case of dermatitis due to merthiolate. The patient was a white man, aged 50, a physician, who had had several attacks of dermatitis due to merthiolate. A few days before examination he had accidentally spilled some merthiolate on his legs. Examination disclosed an erythematovesicular dermatitis which was more pronounced on the outer surface of the left thigh, on the inner surface of the leg near the knee and on the outer surface of the left foot.

Four of our patients who were sensitive to merthiolate (sodium ethylmercurithiosalicylate) gave essentially negative reactions to the simpler inorganic mercurial compounds and also to metaphen (4-nitro-anhydro-5-hydroxymercurioorthocresol), mercresin (amyltricresols and orthohydroxyphenylmercuric chloride) and mercurochrome (disodium salt of dibromoxymercurifluorescein [26.7 per cent mercury]).

REPORT OF CASES

CASE 1.—W. C., a white man aged 42, was first seen in February 1941, complaining of an eruption confined to the right little finger, of two weeks' duration. The eruption had appeared two days after first aid had been applied to a laceration. The entire finger was involved in an erythematovesiculopustular dermatitis. Scrapings were negative for fungi, and cultures showed staphylococci. There was slight enlargement of the right epitrochlear lymph node, but the nodes in the axilla were normal. The patient had a mild, chronic, moderately active dermatophytosis of the feet, and scrapings showed a few yeast cells and myceliums. The lesion on the finger was treated with 2 per cent gentian violet, an oxycholesterol-petrolatum ointment and solution of aluminum acetate soaks. In three weeks the eruption had entirely healed. When he returned to the first aid station to report for work, the finger was painted with tincture of merthiolate. Two days later the entire eruption had recurred. The same form of therapy as previously advised was resumed, and patch tests were made with chromic acid, boric acid ointment, "banderizer," 2 per cent mercurochrome, tincture of metaphen, 10 per cent ammoniated mercury ointment, mercresin, alcohol, benzine and tincture of merthiolate. All the reactions were negative except that to merthiolate. In the test area for merthiolate there was a rapidly spreading erythematovesicular eruption. The area involved was 3 or 4 cm. in diameter, although the patch test was applied to an area 1 cm. in diameter. One month later a patch test was made with a 1:1,000 aqueous solution of plain merthiolate (supplied by E. Lilly & Co.). The next day there was a dermatitis similar to that which followed the patch test with tincture of merthiolate.

Case 1 illustrates a case of occupational dermatitis due to treatment received in the first aid room.

CASE 2.—J. F., a white man aged 41, was first seen in March 1941. He gave a history of a chronic dermatophytosis of the feet which had recently become

16. Robinson, H. M.: Notes on the Commoner Skin Diseases, Baltimore, Chelsea Publishing Company, 1937, p. 112, fig. 4; Practical Dermatology and Syphilis, Philadelphia, P. Blakiston's Son & Co., 1939, p. 123, fig. 95.

activated. He had been applying merthiolate cream and Castellani's carbolfuchsin solution. A week before, a severe, extensive, edematous, erythematovesicular dermatitis developed involving the external genitalia and adjoining regions, the neck, the face and the left thumb. On the neck there were several well defined areas of dermatitis with pustules. Treatment consisted of compresses wrung out in solution of aluminum acetate, tincture of mercresin applied to the pustules and a mild antipruritic ointment. Patch tests were performed with merthiolate cream, mercresin, metaphen, Scott's solution, 10 per cent ammoniated mercury ointment, tincture of iodine, yellow mercuric oxide ointment and a 1:1,000 solution of mercury bichloride. There was slight reaction to the tincture of iodine, to the yellow mercuric oxide ointment and to the ammoniated mercury ointment. At the site where merthiolate was applied there was a severe vesicular reaction within three hours, which spread to cover an area 6 cm. in diameter. Later a patch test with a 1:1,000 unbuffered aqueous solution of merthiolate was performed, and an eruption resulted which was similar to the one caused by the merthiolate cream. Six weeks later tincture of merthiolate was painted on an area 1 cm. in diameter below the bend of the elbow on the flexor surface of the forearm. Within twenty-four hours there was an erythematovesicular dermatitis not only in the area of application but also where the painted skin came into contact with the arm when the elbow was flexed.

Case 3.—A white woman aged 20 had treated dermatophytosis of her feet with tincture of merthiolate. The tincture was applied for two consecutive days, and on the third day an erythematovesicular dermatitis with edema appeared on both feet. She was admitted to the University Hospital, where patch tests were made with tincture of merthiolate, a 1:1,000 solution of eosin, and a 1:1,000 solution of mercury bichloride. Only the tincture of merthiolate elicited a positive reaction, and six months later this antiseptic solution again caused a positive reaction.

Case 4.—L. B., a white woman aged 27, was first seen on Oct. 28, 1941, complaining of an eruption on the left arm and forearm. Two days previously she had painted several abrasions in this region with tincture of merthiolate. On examination, an extensive erythematovesicular dermatitis covered most of the flexor surface of the left upper extremity. Patch tests were performed with tincture of merthiolate, metaphen, furmerane, mercresin, mercarbolide (orthohydroxyphenylmercuric chloride), mercurochrome, Scott's solution, a 1:1,000 solution of mercury bichloride and ammoniated mercury ointment. All gave negative reactions except the test with the tincture of merthiolate, which caused a 3 plus reaction, composed of erythema, edema and vesiculation and covering an area several times larger than that tested. Soon afterward generalized ill defined plaques of acute dermatitis developed, apparently due to the transfer of the merthiolate by the patient's clothing and hands from the sites of the original dermatitis to other parts of the head and body. The patient was hospitalized, and the dermatitis responded rapidly to bland emollients.

Case 5.—T. S., a white girl aged 13, had a severe acute dermatitis on the arms which developed twenty-four hours after application of an ointment for impetigo. Patch tests with 10 per cent ammoniated mercury ointment, a 1:1,000 solution of mercury bichloride and tincture of merthiolate resulted in positive vesicular reactions to all three.

Case 6.—T. S., a white man aged 35, injured his right leg on July 18, 1941. On July 24, 19 per cent ammoniated mercury was applied, and two days later the entire anterior surface of the right leg was covered by an erythematous, moderately vesicular dermatitis. There was no previous history of the use of an inorganic

mercurial. Subsequent patch tests gave the following results: 5 per cent ammoniated mercury ointment, 2 plus reaction; 1 per cent yellow mercuric oxide ointment, 2 plus; 50 per cent mercurial ointment (gray ointment), 2 plus; "alulotion" (ammoniated mercury), 2 plus; 5 per cent ointment of mild mercurous chloride, 2 plus; 3 per cent metaphen solution, 4 plus, and tincture of mercresin, merthiolate and 2 per cent mercurochrome, doubtful reactions. Patches were applied for only twenty-four hours, except in the case of the three solutions which gave doubtful reactions; these were applied for forty-eight hours.

Three other patients who were sensitive to ammoniated mercury ointment gave negative reactions to patch tests with tincture of merthiolate.

COMMENT

Patients may apparently become sensitized to complex organic mercury compounds without reacting to the simple inorganic or to other complex organic mercurials. This suggests that a radical other than the mercury of the compound or the compound in its entirety acts as the sensitizer. Although many hospitals use tincture of merthiolate routinely for preparation of the skin before venipuncture and for preoperative preparation, apparently very few reactors to this antiseptic have been observed. No dermatitis due to merthiolate was observed in 1940 following the preoperative preparation of approximately 5,000 patients at the University Hospital with tincture of merthiolate. Dermatitis due to tincture of merthiolate is apparently severe and protracted, but it undergoes involution when use of the preparation is discontinued and causes no particularly harmful results.

Ingram,[17] in discussing the cause of eczema or dermatitis, stated that the "external stimulus can be anything under the sun, including the sun." The relatively infrequent sensitization to merthiolate demonstrates anew the error of concluding that a drug is not a possible sensitizer because a series of routine patch test gave negative results.

NOTE.—Since this article was submitted for publication Cherry[18] reported a case of severe dermatitis due to merthiolate. Dermatitis in Cherry's case and in case 1 of this report could be classified as an occupational dermatitis, since it followed the treatment of abrasions received while working.

Dr. J. H. Mitchell, in a lecture before the American Academy of Dermatology in New York in December 1941, stated that he had observed a number of cases of severe dermatitis following the treatment of dermatophytosis with preparations of merthiolate.

8 East Madison Street.

244 North Hilton Street.

17. Ingram, J. T.: Definition and Aetiology of Eczema, Brit. J. Dermat. **47**: 502 (Dec.) 1935.

18. Cherry, C. B.: Dermatitis Caused by Tincture of Merthiolate, Arch. Dermat. & Syph. **44**:1105 (Dec.) 1941.

ABSORPTION OF VITAMIN A THROUGH HUMAN SKIN

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It is generally conceded that vitamin A can be absorbed through the skin.[1] However, the only direct evidence for this consists of such animal experiments as have recently been reported by Helmer and Jansen [2] and by Eddy and Howell [3]; in the case of the intact human skin the evidence is more meager. Mackie and Eddy [4] found a rise in the vitamin A level of the blood following the application of cod liver oil to the skin in chronic ulcerative colitis with poor intestinal absorption.

In order to test whether physiologically significant absorption can take place through the human skin, we performed dietary experiments on 17 young men.[5] During the course of dietary vitamin A depletion, ointments containing vitamin A were applied to the skin of the subjects; the status of vitamin A nutrition was studied by means of dark adaptation measurements. The Hecht-Shlaer instrument [6] was used for these measurements. That the course of vitamin A depletion and the recovery from the depleted state may be followed by dark adaptation

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1. (*a*) Eller, J. J., and Wolff, S.: Hormones and Vitamin in Cosmetics, J. A. M. A. **114**:1864 (May 11); 2002 (May 18) 1940. (*b*) Eddy, W. H., and Dalldorf, G.: The Avitaminoses, ed. 2, Baltimore, Williams & Wilkins Company, 1941.

2. Helmer, A. C., and Jansen, C.: Topical Application of Vitamin A, Studies Inst. Divi Thomae **1**:1, 1939.

3. Eddy, W. H., and Howell, J. L.: Topical Application of Vitamin A, New York State J. Med. **39**:406, 1939.

4. Mackie, T. T., and Eddy, W. H.: Clinical Value of Vitamin Determinations, Am. J. Digest. Dis. **6**:617, 1939.

5. The subjects were medical students at New York University. The experiments described in this paper were performed during the winter and spring of 1938-1939.

6. Hecht, S., and Shlaer, S.: An Adaptometer for Measuring Human Dark Adaptation, J. Optic. Soc. America **28**:269, 1938.

measurements has been shown by Hecht and Mandelbaum,[7] Booher, Callison and Hewston,[8] Jeghers,[9] Wald, Jeghers and Arminio,[10] Wald and Steven [11] and other investigators. Certain criticisms which have been leveled at the use of dark adaptation methods in vitamin A studies have concerned the validity of statistics drawn from large survey studies; these do not pertain to dietary experiments. Other criticisms concerning the accuracy of the dark adaptation method have been avoided by the use of the Hecht-Shlaer instrument, which was particularly designed to meet the physiologic requirements for the proper measurement of dark adaptation.

METHOD

During a preliminary period of three weeks, dark adaptation tests were made on each subject twice weekly in order to establish the normal basal threshold level for each one and in order to enable him to become adept in the use of the instrument. The technic used throughout the experiment was that recommended by Hecht and Mandelbaum,[7] dark adaptation measurements being made in a 3 degree test field located 7 degrees temporally to the fixation point. The preadapting intensity was approximately 1,600 millilamberts. The color of the test light was violet. Under these conditions a normal subject gives a dark adaptation curve corresponding to curve *A* in chart 1. This curve is obtained by plotting the minimal perceptible light intensity, or light threshold, during the course of about thirty minutes' dark adaptation after the eye has been exposed to the bright preadapting light. The curve is seen to level off after a few minutes; this level is known as the cone threshold. A second period of rapid dark adaptation commences after from seven to nine minutes, when the rod cells in the retina take over the visual function. The final rod threshold, as obtained after thirty minutes of dark adaptation, may be taken as an index of the status of vitamin A nutrition. This final rod threshold extends over a range of 1 log unit for normal well nourished subjects; within this range there may be no differences in the nutritional status of the subjects. However, for a

7. Hecht, S., and Mandelbaum, J.: The Relation Between Vitamin A and Dark Adaptation, J. A. M. A. **112**:1910 (May 13) 1939.

8. Booher, L. E.; Callison, E. C., and Hewston, E. M.: Determination of Minimum Vitamin A Requirements of Normal Adults, J. Nutrition **17**:317, 1939.

9. Jeghers, H.: Degree of Vitamin A Deficiency in Adults: Note on Experimental Production, J. A. M. A. **109**:756 (Sept. 4) 1937.

10. Wald, G.; Jeghers, H., and Arminio, J.: An Experiment in Human Dietary Night Blindness, Am. J. Physiol. **127**:732, 1938.

11. Wald, G., and Steven, D.: Experiment in Human Vitamin A Deficiency, Proc. Nat. Acad. Sc. **25**:344, 1939.

single person the threshold level will remain constant within 0.3 log unit.[7] During the course of dietary vitamin A depletion the chief change in the dark adaptation curve is the elevation produced in the level of the final rod threshold; a consistent elevation greater than 0.3 log unit above the basal normal threshold level for any subject may be considered significant and indicative of some degree of vitamin A deficiency.

At the end of the preliminary period the subjects were divided into two groups: Group A contained 6 subjects and group B 11 subjects. The mean threshold level for the two groups was approximately the same (table 1).

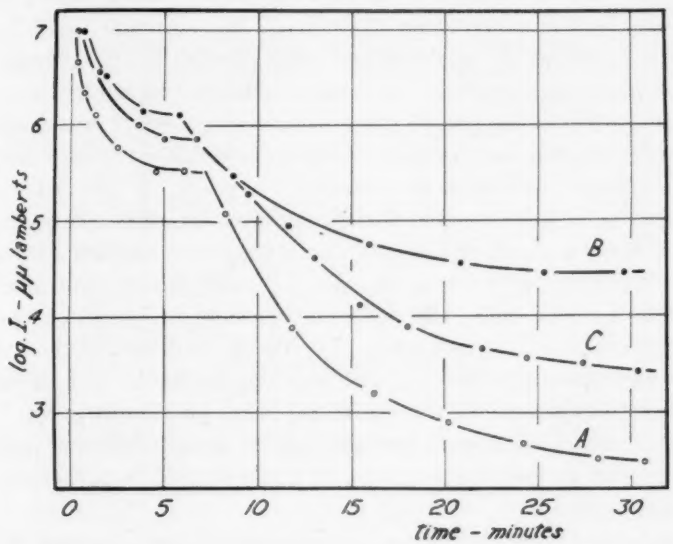

Chart 1.—Three dark adaptation curves given by subject W. L.: *A*, normal curve, at start of the experiment; *B*, at the end of ninety-four days of vitamin A depletion, and, *C*, after forty-two days use of the vitamin A ointment.

TABLE 1.—*Normal Rod Thresholds of Seventeen Subjects*

Group	Rod Thresholds		Weight, Pounds		Average Age
	Range	Average	Range	Average	
A (6 subjects).....	2.45-2.60	2.50	148-177	166	24.5
B (11 subjects).....	2.30-2.95	2.57	146-180	165	24.1

All the subjects were given a vitamin A–deficient diet, planned according to the vitamin content of foods as given by Daniel and Munsell.[12] Dark adaptation measurements were made on each subject

12. Daniel, E. P., and Munsell, H. E.: Vitamin Content of Foods, Miscellaneous Publication 275, United States Department of Agriculture, 1937.

twice weekly throughout the experiment. Supplementary vitamins were given in brewers' yeast and in irradiated ergosterol in order that the picture of vitamin A deficiency might remain uncomplicated by the appearance of other deficiencies. No supplementary vitamin C was given, for an adequate source was allowed in the diet (grapefruit). Daily records were kept of the actual food intake of each subject. The calculated daily intake of vitamin A was well under 150 U. S. P. units daily.

Each of the subjects received daily applications of ointment to the skin of the abdomen. Approximately 6 Gm. of ointment was massaged into the skin for ten minutes. The skin was then covered with a paper towel, which was removed after six hours. The ointment given to the 6 subjects in group A was fortified with 10,000 U. S. P. units of vitamin A per gram, suspended in a base containing hydrous wool fat.[13] The control ointment given to the subjects in group B was made to resemble the vitamin ointment as closely as possible in color, odor and consistency, but it contained no vitamin.

The effect of the vitamin A–deficient diet on dark adaptation is illustrated in curve *B*, chart 1, which shows the course of dark adaptation of one of the subjects in group B (W. L.) ninety-four days after the start of the depletion diet. His final rod threshold is seen to be elevated 2.00 log units above his basal level. During the first part of the experiment the elevations produced in the final rod thresholds for groups A and B were compared. If the elevations were greater in group B, in which the control ointment was applied, it would indicate that the vitamin applied to the skin in group A was effective in preventing the rise in threshold.

During the second part of the experiment subjects in group B who had shown considerable threshold elevations were shifted over to the group receiving vitamin ointment while they continued with the vitamin-deficient diet. The purpose of this was to determine whether sufficient vitamin A could be absorbed through the skin to bring about actual improvement in dark adaptation. Curve *C* in chart 1 gives the dark

13. The formula of the vitamin ointment was:

Hydrous wool fat	225	Gm.
Petrolatum	110	Gm.
Liquid petrolatum	20	cc.
Vegetable oil	20	cc.
Vitamin A concentrate (200,000 U. S. P. units per gram)	25	Gm.
Perfume	2.5	cc.
Water	97.5	cc.
	500.0	Gm.

adaptation curve of W. L. forty-two days after he had been shifted over to the group receiving vitamin ointment. At this time it can be seen that his rod threshold is elevated only 1.00 log unit above his basal level, a recovery of 1.00 log unit having been made.

In chart 2 the threshold levels throughout the experiment are plotted for the 6 subjects who were shifted to the group receiving vitamin ointment. The bottom curve is a composite control curve and is the average for the 5 subjects in group B who were not shifted to the group receiving vitamin ointment; this curve is correctly placed on the

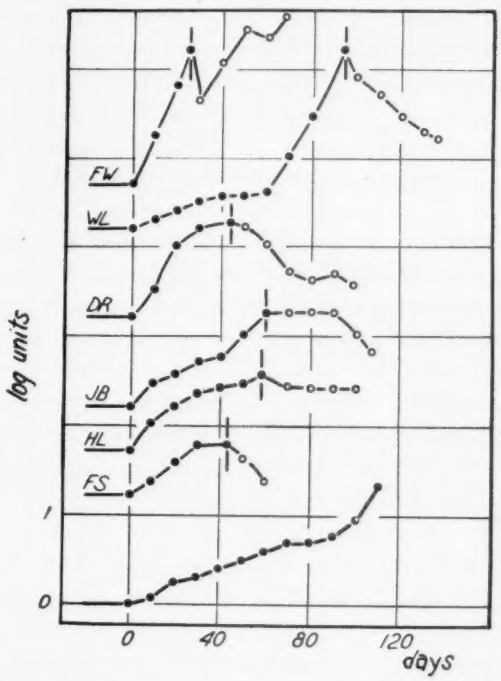

Chart 2.—The course of the rod threshold throughout the experiment for the subjects shifted from the control group to the group receiving vitamin ointment. The lowest curve is a control and is the average for the 5 subjects in group B who continued to use the control ointment throughout the experiment. The other curves are for the 6 subjects who were shifted. These have been displaced vertically, the basal threshold level being indicated in each case. The short vertical lines indicate the time when each subject was shifted to the vitamin ointment. Since dark adaptation measurements were made twice weekly, each point on these curves represents the average of about three tests.

ordinate axis. The other curves have all been displaced vertically in order that they may be studied individually. The basal level for each curve is indicated; here the true ordinate value is zero. The height

of the curve at any point indicates the elevation of the rod threshold level above the basal normal level. The curves through the filled-in circles represent the course of depletion while the control ointment was applied. The time of the shift to the vitamin ointment is indicated in each case by the small vertical line; the subsequent open circles refer to the threshold levels while the vitamin ointment was being applied. The effect of the shift to the vitamin ointment is apparent from this chart. A more detailed analysis of the results of this part of the experiment will be given in the next section.

RESULTS

During the first part of the experiment the subjects continued to receive the ointments assigned to them at the beginning of the experiment. The 11 subjects in group B all showed significant rises in threshold during the experiment (i. e., a rise in threshold greater than 0.3 log unit consistently maintained). The smallest rise was 0.55 log unit, obtained in F. C., who had to stop the diet early in the experiment because of excessive loss of weight. The greatest elevation recorded was for W. L., whose threshold rose 2.00 log units. For the 7 subjects who were carried beyond a 1.00 log unit rise the time required to reach this elevation varied from eighteen to one hundred and ten days. This is fairly consistent with the data of Booher, Callison and Hewston,[8] who reported that their 5 subjects required from five to sixteen weeks to reach this degree of elevation with a similar diet.

In group A only 1 subject, H. K., showed a significant and consistent rise in threshold. The rate of rise of threshold for this subject was comparable to the slowest rate in group B. One subject, B. F., showed a small rise in the beginning of the experiment; however, this was only temporary, and his threshold fell almost to its basal level later in the experiment.

The data for this part of the experiment are presented in table 2. The basal threshold level for each subject is given as well as the levels after thirty-six [14] and eighty-eight days [15] of the depletion diet and at the conclusion of the first part of the experiment. The threshold levels given refer to the average values obtained from several dark adaptation runs, not to single measurements.

At the end of thirty-six days the rise for the control group (including F. W., who had been shifted to the group receiving vitamin ointment

14. At the end of thirty-six days the difference between the two groups seemed to be significant; 3 subjects were shifted to the group receiving control ointment, as will be explained later.

15. Study of the last 3 subjects in group A was discontinued here.

after only twenty-five days) was 0.59 ± 0.11 log unit. For the group receiving the vitamin ointment the rise was only 0.16 ± 0.08 log unit. At this time 9 of the 11 control subjects showed significant rises exceeding 0.03 log unit, while only 2 of the 6 subjects in the group receiving the vitamin ointment showed a rise of this magnitude. B. F. showed a threshold rise of 0.45 log unit, which if consistently maintained would indicate an early state of vitamin A deficiency. This elevation, however, was not maintained, the threshold level falling subsequently to a level only 0.15 log unit above the basal threshold. The subjects

TABLE 2.—*Changes in Rod Threshold (at Thirty Minutes) for All the Subjects During the First Part of the Experiment. Subjects in Group B Received a Control Cream Containing No Vitamin A. Subjects in Group A Received the Cream Containing Vitamin A.*

Subject	Normal Threshold	Rod Threshold 36 Days	Rod Threshold 88 Days	Final Threshold	Total Rise in Threshold	Number Days	Average Change of Threshold *
Group B							
S. K.	2.55	3.05	3.25	3.55	1.00	103	0.97
J. S.	2.95	3.10	4.15	4.65	1.70	109	1.56
D. J.	2.75	3.10	3.35	4.20	1.45	121	1.20
F. C.	2.70	2.95	....	3.25	0.55	47	1.17
W. S.	2.80	3.35	3.55	3.70	0.90	103	0.88
F. W.	2.75	....	....	4.25	1.50	25	6.00
W. L.	2.45	2.80	4.30	4.45	2.00	94	2.13
F. S.	2.60	3.20	....	3.25	0.65	43	1.51
H. L.	2.30	3.00	....	3.15	0.85	59	1.44
J. B.	2.60	3.15	....	3.65	1.05	60	1.75
D. R.	2.35	3.35	....	3.40	1.05	44	2.39
Group A							
H. K.	2.60	2.90	3.20	3.50	0.90	108	0.85
C. C.	2.45	2.55	2.65	2.65	0.20	88	0.23
B. F.	2.45	2.90	2.60	2.60	0.15	88	0.17
F. E.	2.55	2.65	....	2.65	0.10	36	0.28
D. B.	2.50	2.60	....	2.60	0.10	36	0.28
S. G.	2.45	2.35	....	2.35	—0.10	36	—0.28

* × 10^{-2} log units per day.

in the control group who showed small rises at this time continued to give rising thresholds, indicating that even at this time the small threshold rises for these subjects were significant of early vitamin A depletion. H. K. was the other subject in the group receiving the vitamin ointment who showed a rise at this time; his threshold also continued to rise.

After thirty-six days, 3 subjects in group A who had not shown significant threshold rises were shifted over to the group receiving the control ointment in order to demonstrate the rates of rise in their threshold levels when the vitamin was not applied to their skin (D. B., S. G. and F. E.). Unfortunately 2 of these 3 subjects became ill shortly afterward and were advised to stop the experiment (during

this time there was a rather severe epidemic of infections of the upper respiratory tract in the city of New York). Therefore this part of the experiment could not be completed.

At the end of eighty-eight days, of the 3 remaining subjects in group A only H. K. showed a significant rise. The thresholds of G. C. and B. F. had risen only 0.20 and 0.15 log unit respectively. Of the 11 subjects in the control group, 1 (F. C.) had stopped the diet before this time, as was previously explained, and 5 had been shifted to the group receiving the vitamin ointment. These 6 subjects had all shown significant rises before eighty-eight days, varying from 0.55 to 1.50 log units. The other 5 subjects still in the control group all showed significant rises at this time, varying from 0.60 to 1.85 log units, as is evident from the table. The numbers in the next to the last column of the table refer to the number of days the subjects received the ointment originally assigned to them. Because the subjects were taken off the diet or were shifted from the control group to the group receiving vitamin ointment at different times, the average rate of rise of threshold is a more valid index for comparison than is the final threshold rise attained; the average rate of rise in threshold for each subject is given in the last column of the table. In chart 3 these rates are shown for comparison between group A and group B. The eleven black bars indicate the rates of rise of threshold for the subjects in group B, who received the control ointment. The last six white bars are for the subjects of group A, who received the vitamin ointment. In the group receiving the vitamin ointment only 1 subject (H. K.) showed a rise comparable to any of the control rates; the other rates of rise were practically negligible, the actual increments in threshold being within the limits of normal day to day variation. One subject (S. G.) even showed a fall in threshold, signified by a negative rate.

In the second part of the experiment, subjects who showed large threshold rises with the control ointment were shifted to the group receiving the vitamin ointment. The time of the shift was different for each person because of the differences in time required by the subjects to show large threshold rises during the course of depletion. It was not considered desirable to shift a subject to the group receiving vitamin ointment before he showed a threshold rise of 1 log unit. The earliest shift was made in the case of F. W., who reached an elevation of 1.50 log units in only twenty-five days. The last subject to be shifted was W. L., who was allowed to go on to an elevation of 2.00 log units in ninety-four days. F. S. was shifted after forty-three days, when his threshold rise was only 0.65 log unit, because he was to stop the experiment in a short time.

The data for this part of the experiment are shown graphically in chart 2. Of the 6 subjects who were shifted to the group receiving vitamin ointment, 5 showed improving dark adaptation. The sixth, F. W., showed temporary improvement but then continued to show a rising threshold.[16] In chart 3 the white bars in the middle section indicate for each subject the rate of change of threshold after the shift, computed as an average rate for the duration of the second part of the experiment. These rates are readily compared with the rates before the shift, which are given by the corresponding black bars. Negative rates, signifying improving dark adaptation, are plotted here below the horizontal line.

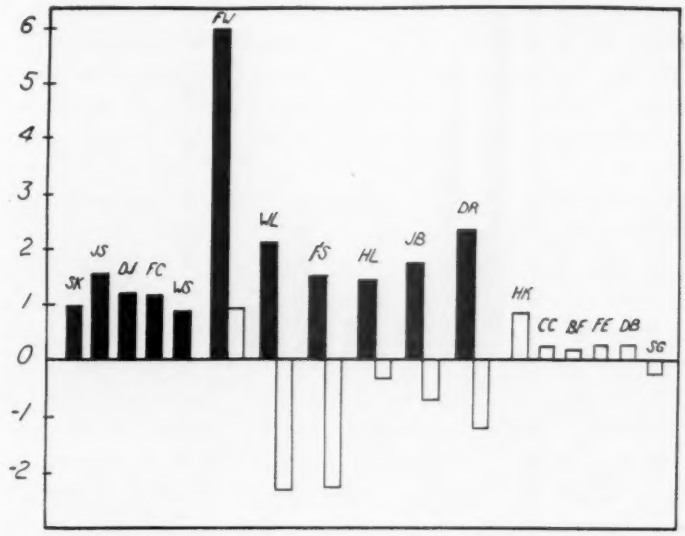

Chart 3.—The rates of change in rod threshold for all the subjects on the vitamin A-deficient diet are indicated by the heights of the bars. Group B, receiving the control ointment, is represented by the black bars; group A, receiving the vitamin A ointment, is represented by the last six white bars. The middle six white bars refer to the subjects in group B who were shifted from the control group to the group receiving vitamin ointment and give their rates after the shifts. A negative rate (below the horizontal line) signifies improving dark adaptation. All the average rates given here are in terms of hundredths of a log unit per day.

The presentation of average rates obtained over a considerable length of time might be objected to on the ground that the rate of depletion need not be linear but might be slow at first and then more

16. At the conclusion of the experiment this subject was given large doses of vitamin A by mouth (100,000 U. S. P. units daily). Nevertheless, his dark adaptation curve did not return to normal until many months had elapsed.

rapid or rapid at first and then slower. Similarly, recovery after the administration of the vitamin might be slow at first and then more rapid, or it might be rapid at first and then slower. These irregularities might mask the effect of the shift to the vitamin ointment. For this reason it is possibly more valid to compare the threshold levels for a shorter period, twenty days before and twenty days after the shift. This is presented graphically in chart 4. The six black bars refer to the rates of change in threshold level while the subjects were using the control ointment during the twenty days immediately preceding the shift. The white bars represent the twenty days immediately following the shift.

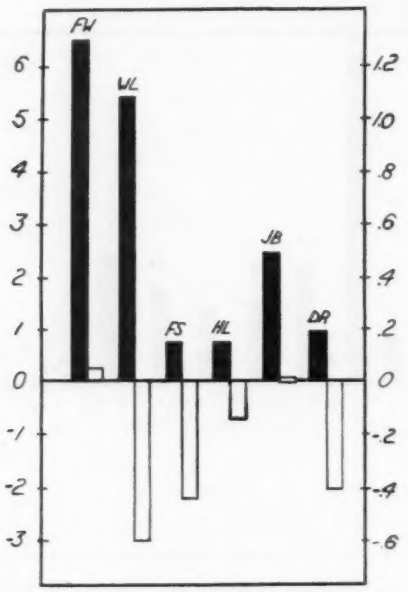

Chart 4.—The rates of change in the rod threshold for the 6 subjects who were shifted from the control group to the group receiving vitamin ointment for the twenty days preceding (black bars) and the twenty days subsequent to (white bars) the change. The ordinates on the left refer to rate of change and are in terms of hundredths of a log unit per day. The ordinates on the right refer to the acutal changes in log units during the twenty day periods. Negative changes, below the horizontal line, signify improving dark adaptation.

COMMENT

The two parts of this experiment have indicated that vitamin A can be absorbed when it is applied to the intact human skin. The vitamin was active in what may be considered a "preventive" capacity during the first part of the experiment, when it significantly diminished the rate of rise of threshold. In the second part of the experiment it was

active in what may be considered a "therapeutic" capacity, improving the dark adaptation in subjects previously depleted of vitamin A.

Physiologically significant quantities of the vitamin had to be absorbed in order to produce these effects. It is probable that the amount of vitamin A absorbed through the skin varies considerably in different persons. In the case of W. L., for instance, the ointment applied to the abdomen was completely taken up by the skin at the end of a few minutes' massage. In this case the most dramatic results were obtained. In the case of the other subjects a varying amount of the ointment always remained on the skin, grossly unabsorbed. It is difficult to arrive at any quantitative estimation of the efficiency of cutaneous absorption in human subjects because of the difference in the rate at which the skin of different subjects took up the ointment in which the vitamin was suspended and also, because of the wide differences that exist among persons in the rate of depletion, as indicated by dark adaptation. We can only estimate that quantities of vitamin A exceeding 3,000 U. S. P. units daily are required to produce the effects we observed.

We applied a statistical method to our data in order to determine rigorously their validity. Fisher's t distribution method was employed.[17] When the rates of rise of threshold for group A and group B were compared, the probability of achieving this distribution by chance was less than 0.01. The distribution of the threshold rises at the end of thirty-six days could have been achieved by chance according to a probability of between 0.01 and 0.02; by the end of eighty-eight days the separation between the two groups could have been achieved by chance according to a probability of less than 0.01. The chance that the changes in threshold produced by shifting the subjects from the control group to the group receiving vitamin ointment were coincidental was less than 0.01; this is true both for the entire period of observation and for the twenty day periods before and after the change.

Apart from the physiologic interest that is attached to the demonstration that vitamin A can be absorbed through the human skin, certain practical applications become apparent. An alternative route to parenteral injection is possible in cases in which intestinal absorption is faulty, such as in chronic ulcerative colitis, diseases of the pancreas and biliary tract and various other gastrointestinal disturbances. Finally, in the treatment of the specific cutaneous lesion of vitamin A deficiency, phrynoderma, it is possible that local application of the vitamin suspended in a vehicle containing hydrous wool fat may give a more rapid cure than oral administration because of the possibility of building up a greater local concentration of the vitamin.

17. Fisher, R. A.: Statistical Methods for Research Workers, ed. 7, Edinburgh, Oliver & Boyd, 1938.

SUMMARY

1. Of our 17 subjects who received a vitamin A–deficient diet, 11 subjects receiving a control ointment containing no vitamin A showed threshold rises equivalent to 0.59 ± 0.11 log unit at the end of thirty-six days, and the 6 subjects who received an ointment containing vitamin A showed threshold rises during this period of only 0.16 ± 0.08 log unit.

2. For the entire duration of the first part of the experiment, varying from twenty-five to one hundred and twenty-one days for the different subjects, the average rate of rise of rod threshold was 0.0191 ± 0.0043 log unit per day for the subjects receiving the control ointment. For the subjects receiving the vitamin A ointment the average rate of rise was only 0.0026 ± 0.0015 log unit per day.

3. For 6 subjects who were shifted over to the group receiving vitamin A ointment after they had become depleted of vitamin A, significant changes were produced in the course of their threshold levels. In 4 cases definite improvement set in. In 1 case the threshold level was stabilized and showed a slight improvement. In 1 case, after a temporary improvement, the threshold continued to rise. During this time subjects still receiving the control ointment continued to show rising thresholds.

CONCLUSIONS

1. Vitamin A can be absorbed through the skin in physiologically significant quantities.

2. An alternative route to parenteral injection is suggested for use in cases in which intestinal absorption is impaired.

3. It is possible that specific cutaneous lesions of vitamin A deficiency will respond favorably to this form of therapy.

Clinical Notes

SEPARATION OF THE NAILS

HARRY E. ALDERSON, M.D., SAN FRANCISCO

Examination of excessively long nails reveals more or less separation from the nail bed. When the skin and nails are inclined to be dry this separation sometimes extends back almost halfway to the lunula. Since women have been cultivating long tapering nails and shellacking them with varnish of various hues, many cases of this condition are being encountered. The shellac dries and greatly hardens the nails, tending to make them form hard, rigid transverse arches and separate mechanically from the distal part of the nail bed. This tendency to separate is increased as the nails grow longer and pressure on the ends, which is exerted by many contacts during a day's activities, produces more leverage. As the shellac is removed frequently with acetone, this oil solvent adds its drying effect to that of the former. Frequently dry epithelial scales and other material accumulate under the nails, simulating onychomycosis, and sometimes mycotic infection becomes established there. The effort necessary to remove this debris tends to increase the separation.

The treatment is obvious, but will the patients take such advice?

490 Post Street.

News and Comment

SECTION ON DERMATOLOGY AND SYPHILOLOGY OF THE AMERICAN MEDICAL ASSOCIATION

Applications for places on the program of the Section on Dermatology and Syphilology of the American Medical Association for the next annual session, at San Francisco in 1943, are now being received. All Fellows of the American Medical Association are eligible. The program is usually assembled in the early part of December. Essayists who are not Fellows of the American Medical Association may be accepted by invitation.

Applications should be addressed to Dr. Nelson Paul Anderson, Secretary of the Section on Dermatology and Syphilology, 2007 Wilshire Boulevard, Los Angeles.

Obituaries

MAX SAMUEL WIEN, M.D.
1895–1942

Max Samuel Wien died suddenly on June 23, 1942, at the age of 46 years, from a cerebral embolism.

He was born in Chicago on Dec. 10, 1895. In 1922 he married Anne Lurie. Besides his widow he leaves two sons, Robert and Byron.

Dr. Wien was graduated from Rush Medical College in 1919. After serving an internship at Cook County Hospital, Chicago, he affiliated himself, in 1922, with the University of Illinois College of Medicine, where he eventually was appointed associate professor in the department of dermatology, a position he held until the time of his death. In addition, he was attending dermatologist at Mount Sinai Hospital, Chicago, until 1933; attending dermatologist at the Michael Reese Hospital, Chicago, at the time of his death, and consulting dermatologist to the Winfield Tuberculosis Sanatorium, Winfield, Ill.

He was at one time president of the Chicago Dermatological Society (1936), and he belonged to various other scientific organizations, including the American Medical Association, the American Academy of Dermatology and Syphilology and the Society for Investigative Dermatology. He was a specialist certified by the American Board of Dermatology and Syphilology.

Dr. Wien was an excellent dermatologist whose teaching was greatly appreciated by his students. He made many contributions to the literature, among them being pioneer work in this country on lymphogranuloma venereum.

Dr. Wien was a sincere friend, possessed of a keen wit and indefatigable energy. These traits, together with his dynamic personality, endeared him to his colleagues, students, patients and friends. His death is a definite loss to all.

MINNIE OBOLER PERLSTEIN, M.D.

MAX SAMUEL WIEN, M.D.
1895-1942

Abstracts from Current Literature

EDITED BY DR. HERBERT RATTNER

CONGENITAL MELANOMA: REPORT OF A CASE IN WHICH ANTENATAL METASTASIS OCCURRED. LEWIS K. SWEET and H. V. CONNERTY, Am. J. Dis. Child. **62**:1029 (Nov.) 1941.

An unusual case of congenital pigmented tumor is reported. The differential diagnosis rested between a congenital nevus complicated by a malignant melanoma or a neurofibromatosis (Recklinghausen's disease) complicated by neurologic sarcoma and congenital nevi. Definite prenatal metastases were present. The largest nevus involved the diaper region and corresponded to what dermatologists term the bathing trunk nevus.

DERMATITIS DUE TO "ANTISEPTIC OILS." JOSEPH H. LAPIN, Am. J. Dis. Child. **63**:89 (Jan.) 1942.

Six infants under 3 months of age presented a contact dermatitis of the face which was caused by "antiseptic baby oil." While not definitely finding the exact cause, the author believes that the offending substance was a hydroquinone used as an antioxidant.

NELSON PAUL ANDERSON, Los Angeles.

THE TITRATION OF TRACES OF REAGIN: A TECHNIQUE OF FLOCCULATION USING MAXIMAL SERUM PROPORTIONS WITH SECONDARY RECOVERY OF ANTIGEN. H. LUND, Am. J. Syph., Gonor. & Ven. Dis. **26**:1 (Jan.) 1942.

This report deals with the experimental findings and the results of a preliminary clinical trial pointing to the possibility of placing the serology of syphilis on a quantitative scale that far exceeds the scope of standard tests.

REUTER, Milwaukee.

THE MANAGEMENT OF NEUROSYPHILIS. B. DATTNER and E. W. THOMAS, Am. J. Syph., Gonor. & Ven. Dis. **26**:21 (Jan.) 1942.

The first task in the management of neurosyphilis is to determine the activity of the actual infection within the central nervous system. This is believed to be of more importance than the determination of the type of involvement of the nervous system. Guides as to the activity of the infection are the appearance of new clinical manifestations and a thorough examination of the spinal fluid.

In cases of untreated syphilis a positive Wassermann reaction of the spinal fluid with negative reactions to other tests does not prove activity. When a positive Wassermann reaction is associated with increased cells or protein, activity must be assumed.

In cases in which specific therapy is being given, normal cell counts and normal protein content merely indicate that the infectious process is inhibited, and it may again become active within six months after treatment is stopped. If the spinal fluid shows no more than 3 or 4 cells per cubic millimeter and definite diminution in protein content six months after treatment has been discontinued, in all probability the activity of the process has been permanently checked.

The advantages of combined fever and chemotherapy in all cases of neurosyphilis with active spinal fluids are outlined. Prolonged chemotherapy after fever therapy is not believed to be necessary in the great majority of cases.

THE ORAL ADMINISTRATION OF ARSPHENAMINE AND NEOARSPHENAMINE IN THE TREATMENT OF EXPERIMENTAL SYPHILIS OF RABBITS. J. A. KOLMER, H. BRAUN and A. M. RULE, Am. J. Syph., Gonor. & Ven. Dis. **26**:63 (Jan.) 1942.

Both arsphenamine and neoarsphenamine by oral administration are therapeutically effective in acute syphilitic orchitis of rabbits.

The single minimal curative dose of arsphenamine and of neoarsphenamine given orally was from three to five times higher than the minimal curative dose by intravenous injection. Both drugs are rapidly absorbed from the gastrointestinal tract, as shown by the high urinary excretion of arsenic.

BISMUTH STOMATITIS AND ALBUMINURIA. E. E. PETERS, Am. J. Syph., Gonor. & Ven. Dis. **26**:84 (Jan.) 1942.

Six patients manifesting simultaneously bismuth stomatitis and albuminuria are reported. Seven patients with less severe complications who were not hospitalized were observed but not reported on. The similarity between the pharmacologic and toxic behavior of lead and that of bismuth is pointed out. Like lead, bismuth may be liberated from tissue storage depots during acidosis. It is suggested that bismuth be administered with caution to patients who are prone to have acidosis.

A NOTE ON THE SURVIVAL OF TREPONEMA PALLIDUM IN PRESERVED CITRATED HUMAN BLOOD PLASMA. J. A. KOLMER, Am. J. Syph., Gonor. & Ven. Dis. **26**:156 (March) 1942.

Fresh citrated human blood heavily seeded with virulent Spirochaeta pallida may undergo spontaneous sterilization in about seventy-two hours when kept at a temperature of 4 to 6 C., so far as S. pallida is concerned. In the case of citrated plasma spontaneous sterilization may occur in about twenty-four hours. The addition of arsphenamine or neoarsphenamine to citrated blood in a final concentration of 1 : 10,000 is completely destructive for S. pallida after an exposure of fifteen minutes at room temperature. This method is advised in case of doubt regarding the possibility of syphilis in donors and especially in the case of "donors of necessity" involving the use of the blood of known syphilitic persons.

AN ANALYSIS OF DEATHS FOLLOWING THERAPEUTIC MALARIA. U. J. WILE and L. K. MUNDT, Am. J. Syph., Gonor. & Ven. Dis. **26**:181 (March) 1942.

One thousand and twenty-six syphilitic patients have been treated with inoculation malaria at the University of Michigan Hospital since 1925. Twenty-nine patients died either during the paroxysms or immediately after their termination —a mortality rate of 2.8 per cent. Thirty-five per cent of the patients treated had dementia paralytica, and these patients accounted for 66 per cent of the deaths. The risk in dementia paralytica is apparently greater than in tabes or other types of syphilis of the central nervous system.

Of the 29 deaths, peripheral circulatory collapse accounted for 12 (41 per cent), pneumonia for 5 (17 per cent), hyperpyrexia for 5 (17 per cent) and suicide for 2 (7 per cent); and there was 1 (3 per cent) case each of erysipelas, vascular accident (cerebral thrombosis), bleeding duodenal ulcer, ruptured spleen and respiratory failure with convulsions.

A NEW PREPARATION OF ANTIGEN FOR INTRACUTANEOUS DIAGNOSIS OF CHANCROIDAL INFECTION. R. B. DIENST, Am. J. Syph., Gonor. & Ven. Dis. **26**:201 (March) 1942.

There are two methods available to confirm the clinical diagnosis of chancroidal infection. One may culture the etiologic agent, Haemophilus ducreyi, from the suspected lesion, or one may demonstrate hypersensitivity by the intracutaneous inoculation of a specific chancroidal antigen. The antigen first used in the United States for the intracutaneous test was described by Cole and Levin.

A new method of preparing Ducrey bacillus antigen is described and has been shown to be satisfactory for clinical use as an adjunct in the diagnosis of chancroid.

THE TREATMENT OF EARLY SYPHILIS BY THE MASSIVE DOSE METHOD. N. E. BERRY, Am. J. Syph., Gonor. & Ven. Dis. **26**:204 (March) 1942.

The author has treated 50 patients with early syphilis with massive doses of mapharsen by the intravenous drip method. His results apparently correspond closely with the results of others using this method, and he feels certain that this method constitutes a real advance in the treatment of this disease.

GASTRIC LESIONS ASSOCIATED WITH EARLY SYPHILIS. F. W. REYNOLDS, Am. J. Syph., Gonor. & Ven. Dis. **26**:218 (March) 1942.

A patient with pyloric obstruction was found to have secondary syphilis with probably syphilitic involvement of the stomach wall. Associated with early syphilis, there may be gastric lesions in the form of (*a*) a superficial gastritis and (*b*) an interstitial inflammatory process with stenosing potentialities.

AGGLUTINATION OF SUSPENSIONS OF BENTONITE BY SYPHILITIC SERA. E. L. BREAZEALE, Am. J. Syph., Gonor. & Ven. Dis. **26**:231 (March) 1942.

Perhaps the most significant recent advance in the serodiagnosis of syphilis has been the widespread recognition of the fact that the tests as employed today are not specific, that in many diseases other than syphilis the serum will frequently cause flocculation of the lyophilic suspension used as antigen.

In the experiment presented, the author showed that syphilitic serums and 0.85 per cent saline solutions with bivalent cations caused the flocculation of suspended particles of bentonite, a highly dispersed clay. Nonsyphilitic serums or physiologic solution of sodium chloride failed to cause similar flocculation.

COMBINED ARTIFICIAL FEVER, CHEMOTHERAPY, AND VACCINOTHERAPY IN THE TREATMENT OF NEUROSYPHILIS. A. MARIN, Am. J. Syph., Gonor. & Ven. Dis. **26**:234 (March) 1942.

This report reviews three and one-half years' experience in the treatment of various types of neurosyphilis.

Artificial fever therapy combined with chemotherapy and with the use of vaccines as an adjunct to the mechanical hyperpyrexia was given to 265 patients, with no deaths.

The following routine of treatment was used: At 7 a. m. the patient received an injection of an arsenical drug and was immediately given a session of five hours of artificial fever with a temperature of 105 F. On the third and fifth days he was given an injection of a fever-producing vaccine (such as colon bacillus vaccine) and of a bismuth compound. The vaccines caused a temperature of 104 F. This procedure was repeated for ten weeks, over which period the patient received a total of fifty hours of artificial fever at 105 F., ten injections of an arsenical drug and twenty injections each of vaccine and a bismuth compound. Treatment was then continued in the outpatient department with a pentavalent arsenical or neoarsphenamine and with a bismuth preparation.

Forty-six per cent of the patients with dementia paralytica obtained a complete remission. Several with tabes were definitely improved. Of 173 patients who received one complete course of hyperpyrexia, vaccines and chemotherapy, the serologic reaction of the spinal fluid became immediately negative in 6 (4 per cent). Of 84 patients who subsequently received twelve months of chemotherapy following artificial fever therapy, the reaction of the spinal fluid became negative in 17 per cent. Of 34 patients who received twenty-four months of chemotherapy following the hyperpyrexia course, the reaction of the spinal fluid became negative in 18 per cent. Three of 9 patients treated for three years have normal spinal fluids.

REUTER, Milwaukee.

POISON IVY DERMATITIS: I. THE DIAGNOSTIC VALUE OF THE PATCH TEST MADE WITH AN ETHER EXTRACT FROM FRESH LEAVES AND STEMS OF THE POISON IVY PLANT. EDMUND L. KEENEY, STEWART SUNDAY, LESLIE N. GAY and KENNETH LYNCH, Bull. Johns Hopkins Hosp. **69**:482 (Nov.) 1941.

The authors conclude that patch tests performed with a 1:25 peanut oil dilution of an ether extract of the fresh leaves and the stems of the poison ivy plant accurately reveal hypersensitiveness in man to the poison ivy plant. The chances of eliciting false positive reactions with the extract are slight.

NELSON PAUL ANDERSON, Los Angeles.

PROPHYLACTIC ORAL THERAPY AGAINST POISON IVY. HERMAN GOLD and PETER MASUCCI, J. Allergy **13**:157 (Jan.) 1942.

The authors administered prophylactic oral therapy to 20 persons known to be susceptible to poison ivy. Their ages ranged from 10 to 34 years. Treatment consisted in swallowing tablets containing 0.5, 2, 5 and 10 mg. of poison ivy oleoresin. The required number were swallowed right after the noon meal. The initial dose was ½ to 1 tablet containing 0.5 mg. The maximum dose reached for all patients but 1 was 15 tablets of 10 mg. each. The final total dose varied from 3,116.75 to 5,984.25 mg.

A variety of eruptions was encountered in all but 4 patients. They consisted of punctate or solid erythema, patchy or diffuse in distribution, that occurred most often on the arms and the chest. An oozing, vesicular dermatitis of the hands occurred in 2 subjects. In 1 subject a localized dermatitis above the wrist assumed the characteristics of a fixed rash that did not disappear until the end of oral therapy. When the dermatitis was severe, the tablets were administered every second or third day or the treatment was stopped for a few days and then resumed at the last dose level without further difficulty being encountered. Pruritus ani occurred in 5 subjects.

There were no gastrointestinal upsets and no urinary complaints. Repeated blood counts and urine studies failed to show any abnormalities.

Seventeen subjects responded to the oral treatment, as shown by a decrease in sensitivity of the skin both to patch tests with the oleoresin and to field tests (exposure to poison ivy plants).

MENDELSOHN, New York.

THE ANTIGENIC RELATIONSHIP OF THE VIRUSES OF MENINGOPNEUMONITIS AND LYMPHOGRANULOMA VENEREUM. MONROE D. EATON, WALTER P. MARTIN and M. DOROTHY BECK, J. Exper. Med. **75**:21 (Jan.) 1942.

A similarity between the meningopneumonitis virus and the virus of lymphogranuloma venereum has previously been noted by Francis and Magill, who were unable to demonstrate any immunologic relationship. The results of studies by Eaton and his associates indicate an antigenic relationship between the viruses of lymphogranuloma venereum and meningopneumonitis. They suggest that the viruses causing certain forms of atypical pneumonia and lymphogranuloma venereum in human beings and psittacosis in birds and other viruses from mice or ferrets should be classified together as a group of agents which are distributed widely in nature and cause infections of diverse character.

CELL STATE AS AFFECTING SUSCEPTIBILITY TO A VIRUS. WILLIAM F. FRIEDEWALD, J. Exper. Med. **75**:197 (Feb.) 1942.

Certain agents, including methylcholanthrene and a mixture of turpentine and acetone, render rabbit skin abnormally susceptible to papilloma virus infection, so that when virus is inoculated into altered skin papillomas appear earlier and in greater number than on normal skin. The preparatory agents bring about epidermal hyperplasia, and the hyperplastic tissue regenerates with greater rapidity when scarified. A practical result of this demonstration is that this method provides a means of detecting amounts of virus which cause no papillomas on inoculation into normal skin.

LYNCH, St. Paul.

THE INFLUENCE OF ARTIFICIAL FEVER ON MECHANISMS OF RESISTANCE. HAROLD V. ELLINGSON and PAUL F. CLARK, J. Immunol. **43**:65, 1942.

Interest in the therapeutic use of the febrile state was aroused when Wagner von Jauregg reported the improvement in cases of tabes dorsalis and dementia paralytica following artificial infection with malaria and suggested that the elevation of temperature was responsible for the favorable influence. Much investigative work has been done regarding the mechanism involved, though much remains to be done before this is clearly elucidated. Ellingson and Clark have carried out a number of experiments and have found that when severe fever, with a temperature near 41.5 C. (106.7 F.), was induced in rabbits during immunization with sheep red blood cells, typhoid vaccines and egg albumin, the specific antibody responses were impaired in varying degrees. More moderate fever, with a temperature near 40 C. (104 F.), induced in rabbits during immunization with sheep red blood cells had no influence on the resulting titers of circulating antibodies. In rabbits already actively immunized against Eberthella typhosa, the induction of severe fever, near 41.6 C., was followed by rapid reduction of antibody titers. Maintenance of fever for periods of eight hours daily on subsequent days held the titers at the lower level. In passively immunized rabbits, fever near 41 C. (105.8 F.) accelerated the decline of antibody titers. Chloride determinations of whole blood made before and after periods of fever reflected a concentration of blood. Complement content of serum of rabbits is either not affected or only slightly depressed during periods of fever. Severe fever induced during the early hours of intracutaneous infection of rabbits with type I pneumococci had no constant influence on the course of the ensuing infection. Phagocytosis of staphylococci by guinea pig leukocytes in the presence of normal serum increased with rising temperatures to a maximum at 40 C., showing a zone of maximal activity from 39 to 41 C. (102.2 to 105.8 F.). Phagocytosis of staphylococci by leukocytes in human blood showed an optimal zone from 38 to 40 C. (100.4 to 104 F.).

THE RELATIONSHIP OF THE ANTIGENICITY, PHYSICAL-CHEMICAL PROPERTIES, AND POLYSACCHARIDE-CONTENT OF TUBERCULINS TO THEIR INTRACUTANEOUS ACTIVITY. JANET R. MCCARTER and DENNIS W. WATSON, J. Immunol. **43**:85, 1942.

The cutaneous tuberculin reaction in man seems to be only quantitatively specific. Two variables exist: the host and the tuberculin. If large enough doses of any one tuberculin are given, reactions occur in practically all children under 3 years of age who have had no known exposure to tubercle bacilli. Furthermore, evidence is given in this paper that similar doses of tuberculins prepared in different ways yield significantly different numbers of reactors in the same population.

Previous work had suggested the possibility that the properties which make one tuberculin more active intracutaneously than another might be correlated with the degree of antigenicity. In view of Seibert's work, it was thought that the antigenicity might be related to the molecular size of the tuberculin protein. McCarter and Watson investigated the physical-chemical properties and the antigenicity of a number of chemically purified tuberculins prepared from avian, bovine and human tubercle bacilli and the relation of these characteristics to the intracutaneous activity of a tuberculin.

They found that the intracutaneous activity of a tuberculin for human beings is directly correlated with its antigenicity. The greater activity of antigenic tuberculins is shown by the larger number of reactors, by the greater speed in the appearance of the reactions and by the larger size of the reactions. As many as 100 per cent of the persons in a rural population with a low incidence of tuberculosis may react to an antigenic tuberculin if readings are taken six hours after the injections.

As a corollary it follows that reactions to human, bovine and avian tuberculin proteins cannot be considered as even quantitatively special unless it can be shown

that the preparations have similar antigenicity and are homogeneous and that early six hour reactions are elicited by antigenic tuberculin proteins and not by tuberculin polysaccharides. The protein present in tuberculin-polysaccharides and in tuberculo-polysaccharides is responsible for any cutaneous activity they may have. Some persons give six hour reactions to nonantigenic tuberculin proteins. The antigenicity of the tuberculin protein is destroyed when the molecule is degraded by heat to a weight of about 6,000, but for molecules of over 12,000 and up to 36,000 the size bears no relation to the antigenicity. The unfolding ensuing on the denaturation of the tuberculin protein molecule by heat does not greatly affect its antigenicity.

CORNBLEET, Chicago. [FROM THE AUTHORS' SUMMARY]

TOXIC DOSE OF MAPHARSEN GIVEN IN INTERRUPTED DOSES. H. J. MAGNUSON and B. O. RAULSTON, Ven. Dis. Inform. **22**:431 (Dec.) 1941.

The maximum tolerated dose and minimum lethal dose of mapharsen given to anesthetized dogs in three daily doses on each of five successive days do not differ significantly from those found by continuous drip administration under identical conditions. The authors concluded, therefore, that the increased tolerance to mapharsen when given by the continuous drip method is the result of spreading the total dose out over a five day period and is not due to the method of administration.

REUTER, Milwaukee.

Society Transactions

BRONX DERMATOLOGICAL SOCIETY

VAN ALSTYNE H. CORNELL, M.D., *President*
HENRY SILVER, M.D., *Secretary*

Feb. 26, 1942

Diffuse Scleroderma and Sclerodactylia. Presented by DR. CHARLES R. REIN.

R. S., a Negro aged 33, a chauffeur, born in the British West Indies and brought to the United States at the age of 2 years, was first seen at Riker's Island Hospital, Riker's Island, N. Y., on Feb. 24, 1942. He was a drug addict (heroin [diacetylmorphine]) from 1935 to 1938.

He states that in June 1930, while he was an inmate of the Hart's Island Branch Workhouse, he noticed on the left shoulder an area of induration about the size of a silver dollar. There was no discomfort except for continuous peeling for about one month. As the peeling subsided the area became discolored, changing from dark brown to white. This period of discoloration lasted for about three months, after which the skin assumed its natural color. The skin of this area then became fissured and increased in thickness until it assumed a hidelike texture. Eventually the skin all over the body underwent the same change. There was some discoloration of the nasolabial folds and of the scrotum. In October 1941 most of the joints began to stiffen and creak. The joints of the fingers became swollen and tender, greatly impairing use of the fingers and causing considerable pain. The patient was treated for rheumatic arthritis, for which he received salicylates. After this treatment the pain subsided, but the contracture progressed until the hands assumed a clawlike aspect. Ulcerations of the second phalangeal joints then occurred. These ulcerations began as tender small vesicles with a clear watery fluid. During the summer of 1941 the patient noticed that he was unable to perspire and he experienced a stinging sensation over the body.

Physical examination showed equal pupils which reacted to light and in accommodation. There was some discoloration of both ears. The nasal mucosa was atrophic, with many greenish scales. The air space was greatly increased (atrophic rhinitis). There was considerable discoloration of the mucosa of both lips. Many teeth had been extracted. The abdomen was slightly rigid. There was no tenderness. The liver, spleen and kidneys were not palpable.

The skin of the entire body is thickened, tough and fissured, as in ichthyosis. Certain areas of the skin are discolored, i. e., the inner angle of both eyes, the nasolabial folds, the clavicular and subclavicular regions and the scrotum; the last is considerably discolored. The hands are swollen. There are ulcerations of the second phalangeal joints. The joints of the fingers, wrist and shoulders are stiff. The joints of the lower extremities are involved in a similar manner. On flexion of the fingers, there is a sound similar to that of the crackling of new leather.

The Wassermann reaction was negative. The basal metabolic rate on Jan. 9, 1942 was +3 per cent and on February 4 —1 per cent. Examination of the blood on Jan. 2, 1942 showed 70.5 per cent hemoglobin, 4,230,000 red cells and 12,600 white cells, with 61 per cent polymorphonuclear leukocytes, 2 per cent basophils, 23 per cent lymphocytes, 12 per cent monocytes and 2 per cent metamyelocytes. Examination on January 30 showed 91 per cent hemoglobin, 4,900,000 red cells and 28,600 white cells, with 80 per cent polymorphonuclear leukocytes, 13 per cent lymphocytes and 7 per cent monocytes. Chemical examina-

tion of the blood showed 142.9 mg. of total cholesterol, 83.3 mg. of cholesterol esters, 11 mg. of calcium and 3.8 mg. of phosphorus per hundred cubic centimeters. The ratio of cholesterol esters to total cholesterol was 58 per cent.

Roentgenograms of the hands showed fragmentation of the tufts of the terminal phalanges of the first, second, third and fourth fingers without evidence of osteomyelitis. There was narrowing of the interspaces between the second and third as well as between the first and second phalanges. Electrocardiographic examination showed a normal sinus rhythm.

The patient has been receiving a high caloric diet, pills of iron, quinine and strychnine, brewers' yeast, nicotinic acid, thiamine hydrochloride and oil rubs of the skin.

DISCUSSION

DR. ADOLPH ROSTENBERG: You will recall a patient, presented before this society a year ago (ARCH. DERMAT. & SYPH. **43**:894 [May] 1941), who showed considerable improvement following treatment with dihydrotachysterol. Several months later I saw that patient, and the apparent improvement was not evident; the scleroderma progressed to such an extent that the patient had to be subsequently hospitalized. Has any one observed favorable results from the use of dihydrotachysterol?

DR. CHARLES LERNER: I can substantiate the fact that dihydrotachysterol has little effect on generalized scleroderma. A patient treated with this remedy for four months was in a worse condition than at the onset of the disease.

DR. FRANK VERO (by invitation): A patient under my care as well as several patients observed at the Presbyterian Hospital failed to show improvement after the administration of dihydrotachysterol. At the clinic the use of vasodilators in cases of scleroderma gave good results. Daily intravenous injections of prostigmine methylsulfate resulted in remarkable improvement in a Negress. After three weeks' treatment the patient was able to close the hand, which she had been unable to do previously; the trophic ulcerations healed, and her condition has generally improved.

DR. ERNST W. NATHAN (by invitation): A patient with scleredema who was recently under my observation was admitted to Mount Sinai Hospital and treated with dihydrotachysterol. Aside from the ease with which the patient could open his mouth, I was unable to see any further improvement during the last year. I have treated some patients with scleroderma with dihydrotachysterol, but I could not observe any definite improvement. I wish to stress the importance of differentiating between scleroderma and scleroderma with sclerodactylia. I found in 2 cases of sclerodactylia some disturbances in the endocrine system which may, if confirmed, allow one to differentiate between these two forms of scleroderma.

DR. SAMUEL M. PECK: It is not my object to defend the therapeutic claims for dihydrotachysterol in cases of scleroderma. It does seem peculiar, however, that capable dermatologists are reporting poor results with this treatment, while capable internists are in a number of instances maintaining the opposite view. Both Dr. Chargin and I have had occasion to observe several patients under treatment with dihydrotachysterol. A young man with generalized scleroderma showed a subjective rather than an objective improvement. The contradictory experiences with this therapy are probably due to the diagnoses made; a number of the conditions which have been labeled scleroderma are in fact scleroderma-like changes as sequelae of a vascular disease. It is probably the vascular component which has been benefited by the dihydrotachysterol.

Aplastic Anemia Due to Arsphenamine; Stomatitis of Unknown Origin.
Presented by DR. ARTHUR SAYER.

V. I., a man aged 50, born in Italy, was admitted to Mount Sinai Hospital in November 1940 on account of diarrhea which had been present for several months. He also complained of soreness and lesions in the mouth which had been present

for about nine months and for which he was treated at another hospital. There the examination showed a normal blood picture. Histologic examination of one of the oral lesions was suggestive of lichen planus. Three months ago he had received six intravenous injections of arsphenamine on the assumption that the oral lesions might have been syphilitic in origin. After the last injection of arsphenamine he became dyspneic and fainted. Examination of the blood showed a severe degree of anemia and leukopenia. The patient was given blood transfusions and injections of pentnucleotide.

Physical examination showed no essential abnormalities except slightly irregular pupils which reacted sluggishly to light. There was a faint systolic murmur present at the apex. In November 1940 examination of the blood showed 35 per cent hemoglobin, 1,500,000 red cells and 2,200 white cells, with 46 per cent polymorphonuclear leukocytes and 40,000 platelets. The clotting time was nine minutes; clot retraction was incomplete after four days. The tourniquet test elicited a positive reaction. Chemical examination of the blood showed 13 mg. of urea nitrogen and 1.17 mg. of uric acid per hundred cubic centimeters. The icterus index was 5 per cent. The Wassermann reaction was negative. The urine gave a strongly positive reaction for arsenic. The Rehfuss test showed no free hydrochloric acid in the stomach. Roentgenograms of the long bones showed moderate thickening of the cortex of these bones.

A diagnosis of aplastic anemia was made on the basis of the examination of the blood, which showed anemia, leukopenia, thrombopenia and no regeneration of red blood cells. It was thought that the aplastic anemia was due to a previously present anemia which was aggravated by the arsphenamine therapy. The liver and spleen were easily palpable at times but were not felt when the patient was discharged from the hospital about two months later. During his stay in the hospital he complained of soreness in the mouth and had bullous lesions and superficial ulcerations on the buccal mucosa of both cheeks. The tongue remained free of bullous lesions. The eruption in the mouth was diagnosed as toxic bullous eruption.

Since the patient was discharged from the hospital he has been treated in the clinic for the aplastic anemia and for the eruption of the mouth. The blood picture has improved, and in November 1941 examination of the blood showed 84 per cent hemoglobin, 5,400,000 red cells and 70,000 platelets. On Feb. 19, 1942 it showed 94 per cent hemoglobin, 3,500,000 red cells, 5,025 white cells and 140,000 platelets. In spite of the improvement in the blood picture there has been no amelioration of the oral symptoms.

At present the patient still complains of the discomfort in the mouth. There is redness and grayish sloughing in an area about 1½ inches (4 cm.) in diameter over the buccal surface of each cheek. During the past month several areas of alopecia areata have developed on the scalp. The patient has been receiving iron therapy and a high caloric and a high vitamin diet.

DISCUSSION

DR. THEODORE ROSENTHAL: Irrespective of the type of anemia present, this case indicates the need for careful thought in making a diagnosis of syphilis. The administration of so potent a remedy as arsphenamine in a case in which the disease is not definitely diagnosed seems unwarranted. If the disease were suspected of being syphilis, the administration of one of the heavy metals would satisfy the requirements of a therapeutic test without exposing the patient to dangers of the arsenicals.

DR. GIRSCH D. ASTRACHAN: I had the experience of treating a patient who presented changes in the blood in the form of leukopenia, with the lymphocytes predominating. I tried a variety of remedies, including extract of liver and vitamins, without succeeding in controlling the condition. Finally, on the advice of Dr. Frances Pascher, I prescribed concentrated bone marrow extract, 3 drops daily. The patient improved rapidly and is now almost well.

DR. ARTHUR SAYER: I think the reason for giving antisyphilitic treatment to this patient was that he had unequal pupils. Of interest is the unusual condition of the mouth. The patient has a recurrent bullous eruption on the buccal mucosae which seems to be a toxic eruption of unknown origin. Thus far it has been impossible to identify the condition.

Erythema Multiforme Bullosum Causing Stricture of the Esophagus. Presented by DR. SAMUEL FELDMAN.

H. B., a clerk aged 32, consulted his family physician on June 12, 1937 on account of constipation and eructation of gas. He was given a restricted diet and was advised to take bismuth and phenobarbital.

The patient returned on June 24 and complained of severe attacks of sneezing. The eyes were swollen, and there was a painful conjunctivitis. There developed an urticarial eruption which almost covered the entire body. Within a day or two the urticarial lesions began to change in character and appearance. Lesions began to make their appearance in the mouth.

When the patient came to me on June 27, there was a polymorphous eruption practically covering the entire body. It consisted of bullae rising on an inflammatory base, lesions of the iris and urticaria-like patches. Scattered among the larger lesions were smaller papules and vesicles. Several broken-down and macerated bullae were seen in the mouth and throat. Two days later the lesions on the mucous membrane of the mouth had progressed so far that the patient had difficulty in swallowing. A clinical diagnosis of erythema multiforme with the possibility of an allergic reaction to phenobarbital was made.

The patient was admitted to the Bronx Hospital on July 2. It soon became difficult for him to swallow even liquids. He was given dextrose solution intravenously, and rectal feeding was instituted. At the hospital a possible diagnosis of pemphigus was made. The Pels-Macht test showed a phytotoxic index of 47 per cent, which apparently substantiated that diagnosis. However, the lesions disappeared after three weeks of hospital care, and the patient was discharged on July 24. Since then he has remained entirely free of eruption.

He felt well until November, when he began to complain of difficulty in swallowing solid foods. This condition became gradually worse, and on Jan. 15, 1938 a roentgenogram revealed a dilatation of the esophagus approximately at its upper half, indicating an obstruction somewhat below the middle portion. A diagnosis of stricture of the esophagus was made.

Treatment consisted of esophageal dilatation by means of metal bougies. At first the procedure was repeated every two days, and then treatments were gradually reduced to one a week. Up to March 19 the patient had received twenty-two treatments. A second roentgenogram showed decided improvement. The patient was entirely well after one and one-half years of treatment.

DISCUSSION

DR. VAN ALSTYNE H. CORNELL: Is this stricture the end result of the drug eruption at the site?

DR. ADOLPH ROSTENBERG: I saw the patient with the acute stage of the eruption, at which time he presented a severe type of erythema multiforme bullosum. The mouth was a mass of bullae, and the patient was extremely toxic. Subsequently there developed lesions simulating pemphigus. However, the eruption cleared in a comparatively short time. I have not seen the patient for the past two years. During the severe attack he may have had some ulcerations in the esophagus which caused this stricture. I do not think drugs had anything to do with it. While I have never encountered a case of erythema multiforme affecting the esophagus, in this case the disease may have caused the stricture.

DR. MAX BERKOVSKY: It is interesting to point out that during the height of the eruption a Pels-Macht test of the patient's blood gave a reaction indicative of pemphigus, and as the condition improved the phytotoxic index approached the normal.

DR. CHARLES LERNER: Was there severe pain on swallowing at the time that the patient had the acute eruption?

DR. SAMUEL FELDMAN: Yes, there was severe pain. The patient could not swallow even water.

DR. CHARLES WOLF: There is no definite proof that the stricture followed the eruption. Esophagoscopy should have been performed at the time to determine structural changes.

DR. SAMUEL FELDMAN: Administration of a test dose might prove that the erythema multiforme was due to phenobarbital, but I should not attempt to prove it. I had a patient at Morrisania Hospital who had an eruption from sulfanilamide. When the eruption disappeared a test dose of 1 grain (0.065 Gm.) of sulfanilamide caused an unusually severe eruption and extreme tachycardia, for which the patient had to be placed in an oxygen tent.

Familial Xanthoma Tuberosum. Presented by DR. ADOLPH ROSTENBERG.

A man aged 45, born in Austria, states that his mother was married three times. He is an offspring of the second marriage and has an older brother and sister who are suffering from the same disease. The children of the first and third marriage are not affected. The mother herself is suffering from xanthelasma and has multiple sebaceous cysts on the scalp. She believes that her mother also had tumors on the scalp. The patient's father is free from any cutaneous ailment. The patient is married and has a daughter aged 12 years who has suffered from atopic dermatitis since early childhood.

The condition began about fifteen years ago. On the right elbow there is a large ringlike patch which is made up of fused subcutaneous nodules, fairly soft to the touch and showing on pressure a saffron red color. The entire plaque is movable and is not adherent to the underlying tissues. On the dorsal surfaces of the hands over the metacarpophalangeal joints there are hard nodular tumors firmly attached to the underlying tissues, each the size of a hazelnut. The patient is also suffering from xanthelasma involving the eyelids of both eyes.

Examination of the blood showed no abnormalities. The cholesterol content of the blood was 500 mg. per hundred cubic centimeters. The urine was free of sugar and albumin. Roentgenograms of the hands showed no changes in the bones.

DISCUSSION

DR. DAVID BLOOM: In this case the disease is most probably transmitted through the father, for it is inconceivable that the disease would not be manifested in the offspring of the mother's two other marriages if the maternal branch of the family were germinally affected. Investigation of the other members of the family would probably reveal the presence of hypercholesteremia with or without cardiovascular involvement. I have had no personal experience with diets, pancreatic extracts or other substances which supposedly influence the fat metabolism.

DR. ERNST W. NATHAN (by invitation): One of the cases of xanthoma tuberosum studied by Dr. Hermann and myself years ago (*Arch. f. Dermat. u. Syph.* **152**:575, 1926) was that of a girl aged 16 with a high degree of hypercholesteremia, especially characterized by an absolutely and relatively high fraction of serum cholesterol directly extractable with ether. One brother of this girl did not have xanthoma but had hypercholesteremia and a high fraction of serum cholesterol that could be shaken out directly with ether, as in the case of the sister with xanthoma tuberosum. The observation is an example of familial hypercholesteremia. The chemical and physicochemical problems involved in the production and formation of xanthomatosis of the skin were thoroughly investigated and were discussed in my paper.

From a clinical standpoint I should like to point out the interesting combination of xanthoma, xanthelasma of the upper eyelids and arcus senilis, a combination that can be found not too rarely in cases of xanthomatosis with hypercholesteremia.

DR. PAUL GROSS: I suggest treatment with the concentrate of soy bean phosphatide, which is a mixture of phospholipids rich in cephalin. Dr. Kesten and I have had satisfactory results with this preparation in reducing abnormally high blood cholesterol values in cases of certain lipid disturbances of the skin.

DR. DAVID BLOOM: I do not believe that the size of the xanthoma tumors can be influenced by diet or medication, for they consist to a great extent of fibrous tissue. Excision followed by dietary measures is the rational treatment of xanthoma tuberosum.

DR. CHARLES LERNER: I should hesitate to excise the lesions over the knuckles because of their proximity and adherence to the tendons. The group of lesions over the elbow, however, can be thus treated, although one might ask what assurance one could have that new lesions would not reform in the area of excision.

Nevocarcinoma. Presented by DR. CHARLES A. GREENHOUSE.

E. S., a man aged 24, came to the Skin and Cancer Unit of the New York Post-Graduate Medical School and Hospital on Feb. 13, 1942, presenting a lesion on the right foot of six months' duration. He states that the lesion appeared following trauma to the foot.

On the large toe of the right foot there is a fungating lesion the size of a hazelnut. The border is rolled, and in the central area there is an ulceration with a grayish membrane and granulation tissue. The entire area is edematous. There are no palpable glands.

The Wassermann and Kahn reactions were negative. Mycologic studies showed no abnormalities. Histologic examination of a specimen taken from the right large toe showed nevocarcinoma. Roentgenograms showed slight irregularity in contour of the terminal tuft and considerable swelling of the soft tissue of the tip of the right toe.

DISCUSSION

DR. CHARLES WOLF: The patient gave a history of an injury. Was there a nevus present prior to the injury?

DR. CHARLES A. GREENHOUSE: The patient was not aware of any lesion on the toe prior to the injury.

DR. CHARLES WOLF: This is a carcinoma, perhaps of nevoid origin. I suggest a surgical consultation as to the question of amputation of the toe. The procedure would depend on the regional involvement. The fact that there are no palpable glands does not exclude metastases.

DR. CHARLES LERNER: The only sensible thing to do, in my opinion, is to amputate the foot at the ankle, if not higher, in order to save the patient's life. At any rate, heroic surgical intervention is indicated in this case, and the quicker it is performed the better.

DR. DAVID BLOOM: I assume that the patient had a subungual nevus without being aware of it prior to the accident.

DR. SAMUEL M. PECK: According to Dr. Pack (Pack, G. T.: Tumors of the Hands and Feet, St. Louis, C. V. Mosby Company, 1939), melanomas of all locations are notoriously radioresistant, and those in the nail bed are much more so. The necessary dose of roentgen rays is so high that it is usually followed by necrosis. He recommends early amputation in cases of subungual melanoma with prophylactic dissection of the regional lymph nodes. Melanomas of the hands and feet can often be treated more conservatively in the early stages by wide local excision. I have had 2 cases in which the lesions have remained without recurrence for from five to ten years respectively.

DR. GEORGE J. SPINNER: A patient with a melanoma who was under my observation was referred to the New York Skin and Cancer Hospital, where a wide excision was made at least 6 inches (15 cm.) above and below the lesion. In six months the child died showing generalized metastases.

DR. CHARLES LERNER: Most authorities state that metastases in cases of melanocarcinoma occur in the glands much later than in the viscera. It has been claimed that the moment ulceration takes place in the original lesion, visceral metastases occur. The question comes to mind: What would this patient gain by being subjected to amputation? If visceral metastases have occurred nothing will help him, whereas if they have not there would be no advantage in amputation of the leg.

DR. CHARLES A. GREENHOUSE: I am still undecided as to what is the proper procedure in this case, since, as stated, visceral metastases occur at the same time that the lesion undergoes ulceration and long before the glands are involved. I expect to report further on this.

NOTE.—After consultation with members of the tumor clinic at the hospital, amputation of the toe, which was recommended, was performed.

A Case for Diagnosis (Lichen Scrofulosorum). Presented by DR. HARRY B. FEILER.

A. Y., a school boy aged 14, came to the clinic of Lebanon Hospital in December 1941 presenting an eruption of a few months' duration. The rash was limited to the trunk and was accompanied by mild itching. The patient had a scar on the right side of the neck and another in the right groin, probably due to healed tuberculous glands. There was also a scar in the lower lumbar region resulting from an operation for Pott's disease. There is no family history of tuberculosis.

At present the eruption consists of small pinkish red and violaceous flat-topped papules. In some areas the grouping simulates pityriasis rosea. There are a few oval patches in the region of the left scapula and below the left clavicle with papules at the periphery with clear centers. In the region of the left hip joint there are a few erythematous patches. One patch is above the pubis and to the right of the midline, and another is in the region of the right sacroiliac joint; they are made up of violaceous flat-topped papules. The color is probably due to trauma. Some of the papules have hairs piercing their centers.

The Mantoux test in a dilution of 1:1,000,000 gave a *2* plus reaction.

Roentgenograms of the lungs taken elsewhere showed arrested pulmonary tuberculosis of the childhood type. Roentgenograms taken at the hospital showed increased hilar and bronchial markings but no calcium deposits or visible swelling of the hilar glands. Therefore, a definite diagnosis of tuberculosis could not be made.

Histologic examination showed a dense, sharply delimited inflammatory infiltrate, mainly in the papillary layer of the cutis. In the deeper portion of the cutis around the hair follicles, sweat glands and blood vessels, scattered collections of inflammatory cells were seen. At one point the superficial epithelium was undergoing necrosis. Vesicle formation was also present between the papillary body and the epidermis. The inflammatory exudate consisted of young fibroblasts, histiocytes and round cells. The collagen in the papillary layer showed edema, granular degeneration and areas of fibrinoid swelling. The histologic picture was consistent with a diagnosis of lichen scrofulosorum.

DISCUSSION

DR. PERRY M. SACHS (by invitation): In the specimen submitted I could not find any tubercles, which one would expect in lichen scrofulosorum. There is a localized acanthosis in the region of a follicle, under which there is a band-like cellular infiltration. This suggests the follicular type of lichen planus.

DR. GIRSCH D. ASTRACHAN: I gained the impression that the patient has typical lichen planus. Shiny, well defined polygonal papules, some umbilicated, and some annular lesions are seen on the chest and back. The group of lesions on the chest, however, is not typical for lichen planus; the condition may be lichen scrofulosorum, and therefore the possibility of a combination of two conditions in a single patient should be considered.

DR. ADOLPH ROSTENBERG: If one considers the lesions on the chest alone, a diagnosis of lichen scrofulosorum must be made purely from a clinical standpoint. There are, however, typical lesions of lichen planus, especially the annular lesions on the back. I always avoid making two diagnoses if one can be made to fit the picture. The only way to decide the diagnosis in this case would be by histologic study.

DR. LOUIS CHARGIN: I can easily see how the clinical picture can fit either diagnosis. If one examines the lesions on the trunk, which are small scaly papules in groups, one gains the impression of lichen scrofulosorum. On the other hand, the annular lesions, the color and the scaling are unlike features of lichen scrofulosorum. On the basis of the clinical evidence present I should favor a diagnosis of lichen planus. Lichen scrofulosorum will have to be ruled out by histologic study.

DR. CHARLES LERNER: Unfortunately this boy does not have a single lesion on the penis or on the buccal mucosa. If he had I am almost certain that most of the members would lean toward a diagnosis of lichen planus. The papules have too pronounced a violaceous color as compared with that usually manifest in lichen scrofulosorum. Also against the diagnosis of lichen scrofulosorum are the numerous discrete and widely separated papules. Lesions of lichen scrofulosorum are usually more apt to appear in oval or in roundish groups, somewhat resembling a corymbiform syphilitic eruption in arrangement. This patient's papules are also too flat and too shiny, and in several of them I have observed definite umbilication. Another feature in this case in favor of lichen planus is the presence of lesions in the lines of scratch marks, whereas with lichen scrofulosorum itching is usually entirely absent or slight if present.

DR. SAMUEL M. PECK: J. Jadassohn used to state that a papular eruption situated below the level of the pelvis in children should always lead to the consideration of a possible tuberculid. It is unlikely that the disorder in this case is lichen planus, because it has failed to become generalized. Another biopsy would have to be made to establish the diagnosis.

DR. ARTHUR SAYER: It is accepted that the one clinical diagnosis which can be definitely verified by biopsy is lichen planus. That being the case, the diagnosis of lichen planus should be readily proved by studying one of the less typical lesions. I am surprised that the pathologist was not able to make a definite diagnosis in this case. I suggest that another specimen be taken for further histologic study. My diagnosis is atypical lichen planus.

DR. HARRY B. FEILER: Judging by the lesions on the upper part of the chest and in association with a history of tuberculosis, one would not expect to diagnose lichen planus. In a case of lichen planus of such long duration there would be pigmentary changes, which are not seen in this case. The histologic examination shows that the infiltrate is located in the deeper portion, around the blood vessels and the sweat glands, as well as in the superficial part of the cutis.

Acanthosis Nigricans. Presented by DR. HENRY SILVER.

B. B., a woman aged 75, was admitted to Mount Sinai Hospital on Aug. 21, 1941. About six weeks previously her hands began to swell, redden and itch. The condition soon spread to other parts of the body, and the skin became intensely pigmented.

The past history is irrelevant except for a tonsillar tumor which was treated by roentgen rays six years ago. The patient's parents died at the age of 86. There are three healthy siblings. She has not suffered from loss of weight, and her appetite has been good. She has had hay fever for the past four years.

The skin of the hands, forearms, cubital fossae, axillas, breast folds, groin and medial aspects of the thighs present various degrees of black and gray discoloration, particularly intense on the neck, in the axillas and in the folds of the breasts. In the areas of deepest pigmentation the cutaneous markings are accentuated. In the axillas, under the breasts and on the forearms there are raised hyperkeratotic plaques which at times show fissuring and crusting. On the palate there are

light red papules, partly confluent. The tongue is red, rough and fissured. The itching is intense at times. Antipruritic remedies were of no benefit. Since November 21 she has been treated at the clinic with vitamin A, 25,000 U. S. P. units per day. After a few weeks the pigmentation became lighter in many places.

Physical examination showed no abnormalities of the heart and lungs. There was slight pressure pain in the mesogastrium.

Examination of the urine showed a faint trace of albumin, no sugar, a few white blood cells, epithelial cells and occasional granular casts. Examination of the blood on December 15 showed 320 mg. of cholesterol, 595 mg. of sodium chloride, 23 mg. of urea and 115 mg. of sugar per hundred cubic centimeters.

Histologic examination by Dr. S. Peck showed moderate hyperkeratosis but no parakeratosis. In one section of the slide there was an area of edema at about the basal layer which somewhat suggested edema seen in lichen planus. The reaction was otherwise limited to the papillary and subpapillary body. The findings were suggestive enough to make a possible diagnosis of lichen planus. The second biopsy specimen, taken on November 27, showed hyperkeratosis with a villiform acanthosis. There were many chromatophores. Practically no inflammatory reaction was seen in the cutis. The diagnosis based on this histologic study was acanthosis nigricans.

DISCUSSION

DR. CHARLES LERNER: The patient told me that she has lost 30 pounds (13.5 Kg.), although she still feels well. She also has some pain in the epigastric region, which I suspect is caused by a developing carcinoma somewhere in the gastrointestinal tract.

DR. ADOLPH ROSTENBERG: I recall a man about the same age as this patient who had obscure gastrointestinal symptoms, but the most careful examination, including roentgen studies, failed to detect a visceral tumor. Acanthosis nigricans subsequently developed. I insisted that the patient was suffering from a hidden cancer. The patient finally succumbed, and the autopsy showed a large carcinoma of the stomach, which was not disclosed by roentgenograms. I feel certain that this woman also has a visceral cancer.

DR. ARTHUR SAYER: This patient has a diffuse neurodermatitis on the forearms, and that is the reason that she complained of itching even before pigmentation was noticed. The development of acanthosis nigricans is usually insidious and is not associated with itching. A patient under my care for psoriasis had lesions of acanthosis nigricans. She was later operated on for a gastrointestinal complaint, and a large carcinoma of the stomach was found.

DR. HENRY SILVER: At present there is no doubt as to the diagnosis of acanthosis nigricans, although a few months ago there was some question because the patient showed an acute inflammatory process which simulated lichen planus clinically and histologically. I agree with Dr. Sayer that the inflammatory process complicates the picture. However, the cardinal symptoms of papillomatosis, pigmentation and hyperkeratosis are present. Whether the tonsillar tumor which appeared some six years ago was part of the picture is difficult to say. There are no signs of an abdominal malignant growth. In this connection O'Leary's observation is interesting (in discussion on Herold, W. C.; Kaufman, W. H., and Smith, D. C.: Acanthosis Nigricans, ARCH. DERMAT. & SYPH. **44**:789-799 [Nov.] 1941). In 3 cases of acanthosis nigricans exploratory laparotomies were made. No signs of malignant growth were found. Six months later malignant abdominal tumors developed in 2 of them, and the patients subsequently died.

Macular Atrophy (Schweninger and Buzzi Type). Presented by DR. ARTHUR SAYER.

S. E., a woman aged 25, came to the clinic of Mount Sinai Hospital in 1937, presenting several groups of elevated tumor-like lesions on the skin of her back. The mother states that these lesions had been present for over five years and gradually became more elevated.

The patient is a well developed and well nourished adult who has been mentally retarded since infancy. She has a suggestive microcephalic head and had epilepsy in infancy. There is a history of an injury to the brain at birth, which may be responsible for the mental retardation.

There are about fifty moderately elevated whitish lesions the size of a pea, most of which are in small groups. The overlying skin appears normal. The lesions are moderately soft and can be depressed below the surface with the tip of the finger. There are no definite hernial rings felt in the base of these lesions. There are no subjective symptoms.

The patient has been under observation for about five years. During this period about eight or ten new lesions appeared on the back and abdomen. These new lesions were faintly red at first and then became white and gradually more elevated after several weeks.

The urinalysis showed normal results. The Wassermann reaction was negative. The basal metabolic rate was + 9 per cent. Examination of the blood, including chemical examination, showed no abnormalities.

Histologic examination showed the epidermis to be somewhat atrophic. The papillary bodies were flattened in places; otherwise the epidermis showed little change from normal. There was practically no inflammatory reaction in the cutis. The elastic tissue was missing for the most part, and what was left was fragmented and clumped.

VAN ALSTYNE H. CORNELL, M.D., *President*

HENRY SILVER, M.D., *Secretary*

March 26, 1942

Bullous Eruption Following Sulfanilamide Therapy. Presented by DR. DAVID BLOOM.

W. M., a Negro aged 16, was treated during January 1942 at the clinic for genitourinary diseases of the Sydenham Hospital for gonorrheal urethritis. He received sulfanilamide, 0.5 Gm. four times a day for nineteen days and three times a day for seven days, amounting to a total of approximately 48 Gm. within twenty-six days. On February 1, two days before admission to the hospital, the patient noticed swelling of the upper lip and the appearance of an eruption on the wrists, which soon spread over the body.

On admission to the hospital on February 3, the patient felt sick, had a temperature of 103 F. and presented a generalized eruption, which consisted of papules and vesicles, involving also the mucous membranes of the lips and mouth. The conjunctivas were chemotic, and the corneas were a little hazy. General medical examination revealed no abnormalities.

Urinalysis showed no abnormalities. Examination of the blood showed 78 per cent hemoglobin, 4,000,000 red blood cells and 11,000 white blood cells, with 25 per cent band forms, 61 per cent segmented polymorphonuclear leukocytes, 2 per cent eosinophils, 5 per cent lymphocytes and 7 per cent monocytes. Chemical examination of the blood showed 15.8 mg. of urea nitrogen, 153 mg. of cholesterol, 56 mg. of cholesterol esters and 503 mg. of chlorides per hundred cubic centimeters. The icteric index was 6. A culture of the blood was sterile. The blood level of sulfanilamide was 0.8 mg. per hundred cubic centimeters.

During the next few days the condition of the patient became worse. The temperature rose to 106 F. and then varied between 103 and 105 F. The pulse became weak and irregular. The systolic blood pressure was 116 and the diastolic 70. The eruption changed from papules to vesicles and bullae, from which a trace of sulfanilamide was recovered. While the urea nitrogen level in the blood remained normal, the cholesterol content fell to 122 mg. per hundred cubic centi-

meters and the cholesterol esters to 38 mg. He was treated with infusions of 5 per cent dextrose in saline solution, blood transfusion, intravenous injections of calcium gluconate and instillation of atropine sulfate solution into the eyes. Externally, wet dressings and gentian violet were applied to the denuded areas.

On the fifth day after admission the patient became maniacal and uncontrollable, necessitating the use of sedatives. He showed Cheyne-Stokes respiration, vomited blood and passed blood from the bladder and rectum. The nose and mouth became clogged with mucus and required frequent aspiration. The patient seemed to be near death. The attending internist considered the possibility of sepsis being superimposed on the drug effect and advised that sulfathiazole be given in a dose of 2 Gm. followed by 1 Gm. every four hours. A total of 19 Gm. was given. There followed gradual improvement of the general condition as well as of the eruption. The patient was discharged from the hospital on March 16.

The skin shows numerous hyperpigmented macules the size of a dime or larger and a moderate number of depigmented areas. On the dorsum of the left hand there is a large plaque of depigmentation with some keloid formation. The lesions of the eyes have completely resolved.

Examination of the blood on March 16 showed 69 per cent hemoglobin and 199 mg. of cholesterol and 75 mg. of cholesterol esters per hundred cubic centimeters.

DISCUSSION

DR. FRANK E. CROSS: In view of the reaction to sulfanilamide, it was rather heroic treatment to administer sulfathiazole. However, in the presence of septicemia following the bullous eruption, I feel certain that this measure saved the patient's life.

DR. THEODORE ROSENTHAL: I had the opportunity to see this patient while he was in the hospital and must say that I never saw a more fulminating example of generalized cutaneous involvement. He was in an extremely serious state for about ten days. I can only emphasize what Dr. Bloom has indicated, that internists are not as familiar with the picture of such toxic eruptions as are dermatologists, which probably accounts for the fact that sulfathiazole was administered. I think it is worthy of comment that sulfathiazole apparently did not aggravate the patient's condition. It is a mystery to me that the boy survived in spite of and not because of sulfathiazole. To revert to the treatment of the gonorrheal urethritis, the therapy was antiquated. Modern therapy for this condition consists of 2 Gm. of sulfanilamide a day for ten days or 4 Gm. daily for five days, which is sufficient to cure 90 per cent of infections.

DR. H. VICTOR MENDELSOHN (by invitation): I saw the patient when he first came to the clinic. The eruption presented a bizarre appearance which did not seem to fit in with any of the known dermatoses. This, together with the history of ingestion of moderate doses of sulfanilamide over a period of three to four weeks, strongly suggested the diagnosis of sulfanilamide eruption. Further observation of the patient during his stay in the hospital convinced me that the cutaneous and systemic reactions were manifestations of a specific hypersensitivity to sulfanilamide. The administration of sulfathiazole to the patient during the height of his illness is interesting. It was indeed a daring and risky type of treatment. However, since there were no ill effects and rapid recovery followed, it is reasonable to assume that the patient was hypersensitive to sulfanilamide but not to sulfathiazole. Such an occurrence is not unusual. Instances of intolerance to a certain drug, for instance arsphenamine, and tolerance to one of the same family, neoarsphenamine, are known. The same undoubtedly is true of the sulfanilamide drugs. M. H. Goodman and R. D. Arthur (ARCH. DERMAT. & SYPH. **43**:692 [April] 1941) reported a case of a fixed and papular eruption in a young Negro due to sulfanilamide. The eruption recurred three times with the administration of sulfanilamide but was not provoked by sulfapyridine.

In my opinion, the administration of sulfathiazole had little or nothing to do with the recovery of the present patient.

DR. ARTHUR SAYER: I believe the presenter has omitted one important point in the history which it is necessary to clarify. I refer to blood cultures during the height of the illness. Blood cultures should certainly have been made at that time. I am thinking of the possibility of septicemia, due either to staphylococci or to streptococci from the infected bullae, or possibly of a gonococcic septicemia, as a complication of the gonorrheal urethritis. If septicemia were present sulfathiazole would have been an important therapeutic measure in the cure of the disease.

DR. SAMUEL M. PECK: Patients with a history of familial allergy, the so-called atopic group, are considered by some allergists to be more prone to sensitization. I do not believe that this applies to drug eruptions. At least statistically or experimentally this has never been brought out. However, while I believe that drug eruptions are specific, in a case of a severe reaction to a drug I should hesitate to expose the patient to chemically allied compounds.

DR. THEODORE ROSENTHAL: With respect to blood cultures, it can be stated that these would have been valueless since the bullae had a high sulfanilamide content. The case presented demonstrates the cutaneous manifestations of sulfanilamide. Another complication to consider is the precipitation of conjugated derivatives of sulfanilamide in the renal glomeruli. The history of administration of sulfathiazole in this case after a most severe toxic reaction to sulfanilamide is merely another reason for wonderment as to why the patient is alive today.

DR. GIRSCH D. ASTRACHAN: The question should be clarified as to whether one sulfanilamide drug sensitizes the patient to another. It is known that arsphenamine may act that way, that is, a patient may tolerate one arsphenamine compound and have a reaction to another and then become sensitive to the first one.

DR. DAVID BLOOM: In this case a number of interesting points are presented. The fact that the patient's condition did not get worse after the administration of sulfathiazole indicates that one may be sensitive to one member of his group of drugs and not to the others. The reason the internist administered sulfathiazole was probably that he was awed by the severe illness of the patient and was not willing to attribute such severe illness to involvement of the skin alone. He suspected a septic process, although there was no definite proof for it. The dermatologist, however, has reason to believe that severe changes in the skin may be sufficient to disturb important chemical and metabolic processes in the body so as to endanger life. To prevent such serious reactions, patients should be questioned before the administration of a sulfanilamide compound in regard to hypersensitivity in general and to this drug in particular. They should be closely observed during the course of treatment with regard to changes in the blood and in the skin.

Syphilitic Ulceration Associated with Osteomyelitis. Presented by DR. GIRSCH D. ASTRACHAN.

F. W., a man aged 22, was previously presented at the meeting of the American Academy of Dermatology and Syphilology on Dec. 16, 1941 (ARCH. DERMAT. & SYPH. **45**:623 [March] 1942).

The case is presented again to show the results of local sulfathiazole therapy.

DISCUSSION

DR. THEODORE ROSENTHAL: An ointment containing 5 per cent of sulfathiazole was employed. I should like to know more about the vehicle. Sulfathiazole is an insoluble substance, and I am unable to see how enough of it was absorbed to be effective therapeutically. Sodium sulfathiazole is a much more soluble compound.

DR. ARTHUR SAYER: The diagnosis of syphilis can be readily accepted in this case, but I doubt the effectiveness of sulfathiazole on syphilitic lesions. The drug acts favorably on local staphylococcic infections, and the healing that occurred

was due to a superimposed staphylococcic infection. I have observed cases in which impetigo was treated with sulfathiazole or sulfanilamide and severe irritation of the skin resulted. I think the use of sulfathiazole externally is not absolutely harmless.

DR. FRANK E. CROSS: If the dark field examination showed spirochetes in this case, then the patient probably has a chancre of the big toe. The benefit from sulfathiazole therapy can be explained on the basis of a superimposed secondary infection.

DR. SAMUEL FELDMAN: In connection with the absorption of sulfathiazole through the skin, I should like to cite an illustrative case. After the use of a sulfathiazole ointment locally there developed a generalized eruption. After this eruption subsided, the patient was given 15 grains (1 Gm.) of sulfathiazole by mouth. The eruption reappeared in a severe hemorrhagic form. This indicates that there was absorption of the drug from the site of application. Only in that manner could a vascular sensitization occur.

DR. LEO SPIEGEL: This patient is evidently suffering from syphilis complicated by an osteomyelitis. The question is whether the osteomyelitis is a syphilitic process or due to some other cause. If the sulfathiazole favorably influenced the condition, then the osteomyelitis is due to a disease other than syphilis. I do not think the osteomyelitis in this case is specific.

DR. MAURICE UMANSKY: I have seen a systemic reaction in a patient who was treated locally for a wound on the finger with sulfanilamide powder. This reaction expressed itself in a generalized pruritus, which lasted as long as the powder was applied. As soon as the use of the powder was discontinued the pruritus promptly disappeared.

DR. ARMOND L. LEIBOVITZ (by invitation): In a discussion of this case with the roentgenologists, it was pointed out that the presence of proliferation and destruction of bone, with an outpouching of what appeared to be normal bone between areas of bone destruction, leads one to suspect syphilitic osteomyelitis. However, the considerable destruction of tissue points more toward a diagnosis of pyogenic osteomyelitis. The second roentgenogram, taken in December, showed an increase in density of the bone and absence of spicules and thus indicated that the lesion responded to antisyphilitic therapy. Because of this response the consensus favored syphilitic osteomyelitis.

The sulfathiazole ointment, as made up by the hospital pharmacist, consists of 10 Gm. of powdered sulfathiazole in 30 Gm. of base to which 50 cc. of water is added. The base is made up with the unsaponified fraction of hydrous wool fat dissolved in liquid petrolatum, paraffin and petrolatum. To this 2 per cent of cholesterol is added.

DR. GIRSCH D. ASTRACHAN: At the time of the first presentation the majority of the discussers agreed that syphilis was the cause of the ulceration. It was agreed that the osseous involvement was also due to syphilis. At that time I expressed the opinion that the destruction in this case was due to syphilis and was accelerated by the concomitant Vincent's infection. The patient was treated for some time with bismuth and mapharsen combined with fever therapy. No improvement resulted. Finally, an ointment containing 5 per cent of sulfathiazole was applied locally and antisyphilitic therapy continued. Since then there has been remarkable improvement. I do not think that the improvement is due solely to the sulfathiazole ointment, because roentgenograms of the toe taken before the ointment was prescribed showed the beginning of improvement of the condition. The question of the possibility of toxic effects of sulfanilamide compounds was considered, and blood counts were made before the patient was discharged. There was no change. I do not believe the patient had a chancre on the toe. He had a penile lesion at the beginning of the disease, and the eruption on the toe appeared a few months later. I think this lesion was a form of malignant syphilis, probably late secondary or precocious tertiary.

A Case for Diagnosis (Chronic Lymphedema). Presented by DR. ARTHUR SAYER.

D. C., a woman aged 41, born in Austria, presented herself at the Morrisania Hospital on account of diffuse swellings of the forearms, hands, legs and knees. She states that about twenty years ago the right forearm first became involved and gradually the other regions mentioned became affected. Her general health has always been good, and there is no history of any illness to which this condition could be ascribed.

The right forearm and right hand are diffusely swollen and are about twice the normal size. The swelling begins at the elbow and extends to the proximal interphalangeal joint of the hand. The distal portions of the fingers taper to normal size. The overlying skin is normal. There is only slight pitting on pressure. There is no evidence of fluid in the elbow or wrist joints. The left forearm and left hand are involved to a lesser degree, and this extremity is also diffusely swollen from the elbow to the proximal interphalangeal joints. This extremity feels somewhat softer than the corresponding right extremity. The legs are moderately swollen from the knees to the ankles. The feet are not swollen. There are lobulated swellings around the knees. The motion of the knee joints and ankle joints is normal, and there is no limitation in any direction.

Roentgenograms of the forearms, hands, legs and feet showed no evidence of pathologic changes in the bones or joints. There was considerable swelling in the soft parts, especially around the wrists and hands. Urinalysis showed a specific gravity of 1.008, a faint trace of albumin and no sugar. The Wassermann and Kahn reactions were negative.

Chemical examination of the blood on fasting showed 10.5 mg. of urea nitrogen, 91 mg. of sugar and 176 mg. of cholesterol per hundred cubic centimeters. A hemogram showed 70 per cent hemoglobin, 4,000,000 red blood cells and 8,000 white blood cells, with 64 per cent leukocytes and 36 per cent lymphocytes. The basal metabolic rate was + 6 per cent.

On March 6, 1942, a medium-sized needle was inserted into the swelling on the posterior region of the left knee, and 100 cc. of clear yellowish fluid was readily aspirated. The patient felt considerable improvement after the aspiration. On March 20, 75 cc. of clear yellowish fluid was again aspirated from the posterior aspect of the left knee.

DISCUSSION

DR. ARTHUR SAYER: I believe that in spite of the fact that there is no family history, this lymphedema should be classified as Milroy's disease. It is possible that the patient is the first member of the family to show the disease. I do not know of any other disease entity which produces this type of chronic lymphedema. There is no hisory of filariasis.

A Case for Diagnosis (Pemphigus Erythematodes? Dermatitis Herpetiformis?). Presented by DR. CHARLES R. REIN.

Mrs. M. M., aged 31, of Italian parentage, presented herself at the Skin and Cancer Unit of the New York Post-Graduate Medical School and Hospital. She states that she was well until six months ago. After the birth of her third child there appeared numerous "blisters" on the legs. Within a few days similar lesions were noticed on the trunk, face, scalp and upper extremities. Physical examination showed nothing abnormal except a persistent vaginal discharge (trichomonas).

Scattered over the face are numerous discrete and confluent erythematous and edematous discoid lesions the size of a dime. The lesions on the nose and malar regions coalesce and present a butterfly appearance. The borders of the lesions are more erythematous than the centers and are slightly raised. Most of the lesions are covered with an adherent greasy crust or scale. On the trunk, most conspicuous on the shoulders, the lumbosacral area and the buttocks, are groups

of subsiding pigmented lesions which began as vesicles and bullae. There are a number of excoriations scattered over these areas. There are a few crusted lesions still present in the involved areas.

A specimen of tissue removed from the left cheek and submitted for histologic examination to Dr. Egbert J. Henschel showed several small bullae containing serum high in the epidermis. A moderate round cell reaction was seen about the blood vessels in the upper part of the cutis. The elastic tissue was preserved. No basophilic degeneration was observed. The histologic diagnosis was pemphigoid bullous eruption.

Patch tests performed with a solution of potassium iodide, furnished by Dr. M. Jessner, on normal skin, over an active lesion and in a pigmented lesion gave negative results.

Examination of the blood showed 83.3 per cent hemoglobin, 4,310,000 red blood cells and 6,350 white blood cells, with 56 per cent polymorphonuclear leukocytes, 35 per cent lymphocytes, 4 per cent eosinophils, 4 per cent monocytes and 1 per cent basophils.

The patient received intramuscular injections of 1 cc. of crude liver three times a week, with little benefit. On March 9, 1942 sulfadiazine (2-[paraaminobenzenesulfonamido]-pyrimidine) therapy, 7½ grains (0.5 Gm.) three times a day, was instituted. Improvement was noted on March 20, at which time the blood sulfadiazine reading was 9.85 mg. per hundred cubic centimeters. The patient is now receiving 15 grains (1 Gm.) of sulfadiazine per day, with continued improvement.

DISCUSSION

DR. ADOLPH ROSTENBERG: I believe the disease in this case is herpes gestationis, which I consider a form of Duhring's disease. My reason for this diagnosis is the fact that the symptoms began after delivery, although six weeks afterward. It is true that this is a rather long period, but such cases have been reported. In these cases the late appearance has been explained by the fact that gonadotropin, which is always present during pregnancy, is retained for a long period after delivery. This hormone has been suspected as the etiologic factor. The result of the therapy makes me more certain that the patient has dermatitis herpetiformis (Duhring's disease), because in all cases in which there is a question between pemphigus and Duhring's disease, the latter improves with sulfanilamide or one of its derivatives and pemphigus does not. This fact could almost be used as a diagnostic criterion.

DR. FRANK E. CROSS: I think that Dr. Rein's first diagnosis is probably correct. I believe this case is a typical one of the Senear-Usher syndrome. I do not think the distribution or the type of lesions conforms to herpes gestationis, which appears much sooner after termination of pregnancy.

DR. WILBERT SACHS: One cannot make a positive diagnosis from the sections submitted. However, there is a small area which is suggestive of an epidermic bullous lesion. This would not fit in with the picture of dermatitis herpetiformis. It may be the explanation for the positive Nikolsky sign.

DR. CHARLES R. REIN: This patient had received treatment with an extract of adrenal cortex (eschatin) for four weeks, during which time there was an exacerbation of the dermatosis.

Chronic Dermatitis of the Hands Due to Shoe Polish. Presented by DR. MAX BERKOVSKY.

S. L., aged 21, a student, had suffered from an eruption of the hands since 1936. He had been treated without apparent benefit. The lesions improved during the summer months and recurred in the fall and winter.

The hands, extending down to the finger tips, were erythematous, dry and scaly. The toes were not involved.

Contact dermatitis was suspected, and patch tests with various contactants were performed. There was a strongly positive reaction to brown shoe polish. The patient stated that he frequently polished his shoes and often tightened the shoe laces during the day. During the summer months he wore white shoes or sandals; hence the resultant amelioration of symptoms. The reaction to a trichophytin test was negative.

He was advised to change to suede shoes, and without local therapy the hands improved considerably. A few weeks later there was a slight exacerbation, though the patient stated that there had been no contact.

The Griffin Shoe Polish Company, when asked for the constituents of their product, submitted the following formula: carnauba (wax), pure sweet spirits of turpentine, a solvent and an intermediate dye.

Book Reviews

Dermatologic Therapy in General Practice. By Marion B. Sulzberger, M.D., and Jack Wolf, M.D. Second edition. Price, $5.00. Pp. 632, including index, with 67 illustrations. Chicago: The Year Book Publishers, Inc., 1942.

The second edition of the excellent book by Sulzberger and Wolf supplies a large amount of useful practical information for the general practitioner and dermatosyphilologist in the treatment of the common cutaneous diseases and syphilis. It is also arranged in a manner to include the necessary facts in regard to etiology and diagnosis without interfering with the essential object of the book, namely, dermatologic therapy.

The problems of treatment discussed go far beyond the average dermatologic textbook in supplying the general management and details of treatment procedures. The recent advances in dermatologic therapy are included, especially in regard to oral and local administration of sulfanilamide and its derivatives and the several forms of intensive arsenical treatment of early syphilitic infection.

The material is presented in a clear, concise manner; thus the volume will be especially valuable to physicians and surgeons in the armed forces, who of necessity will welcome this practical approach to some of their urgent dermatologic problems. These include the modern treatment of burns, cutaneous damage from vesicant gases, various types of dermatitis venenata due to plants, infestations with animal parasites and the prophylaxis and treatment of venereal diseases.

In the chapter on general dermatologic management by physical agents (page 79) the so-called carbon dioxide slush treatment for acne is given too prominent a place in view of the fact that few dermatologists believe that it is of any value in the treatment of this disease.

The volume contains good illustrations of cutaneous diseases and treatment procedures. There is a good index, and a cross index makes desired information readily accessible.

Serology in Syphilis Control; Principles of Sensitivity and Specificity. With an Appendix for Health Officers and Industrial Physicians. By Reuben L. Kahn, M.S., D.Sc. Price, $3.00. Pp. 191. Baltimore: Williams & Wilkins Company, 1942.

As the author states, the text of this little volume deals with principles of sensitivity and specificity with special reference to syphilis control. It does not deal with technic. He emphasizes the value of serology in any syphilis control program. A definition is given of what is meant by sensitivity and specificity in serology, and the statement is made that it is impossible to aim at 100 per cent sensitivity in syphilis.

Some of the historical data leading up to precipitation reactions and to flocculation tests are reviewed.

Kahn doubts the value of multiple tests but brings out the usefulness of quantitative serologic reactions. The Kahn verification test is also discussed.

There is an appendix for health officers and industrial physicians, covering, among other things, blood testing, evaluating serologic tests and laboratories and eliminating technical errors.

Abstracts are also added of some addresses given at a conference on "Serology in Syphilis Control and the Industrial Physician."

The volume may be of value to the serologist, the public health worker and the physician interested in syphilis control.

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